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ASPECTS OF CARBOHYDRATE AND FAT METABOLISM *

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IT WOULD be a very easy matter to discuss recent work on carbohydrate and fat metabolism at great length from the experimental point of view. There are also numerous points of considerable clinical interest. I might gather these latter together and refrain from any description of our own researches, but this would not be fulfilling the obligation which I was very pleased to accept when invited to present this paper. I will, however, compromise and discuss briefly certain general aspects of the subjects and also the results of some investigations which we are at present pursuing.

In the short time at my disposal a few comments on the various phases from the ingestion to the final disposition of the carbohydrate will have to suffice. It is now a matter of common occurrence to observe the great rapidity with which ingested carbohydrate can be absorbed. The effect on blood sugar can actually be detected within a minute or two after the sugar enters the duodenum. Clinicians observe the results of this phenomenon when ingested sugar dramatically relieves insulin hypoglycemia. Cori's recent work (1931) indicates that the different monosaccharides are absorbed at a characteristic and constant rate which is independent of the concentration of the monosaccharide in the intestine. This is quite different from the rate of absorption of the same sugars administered intraperitoneally (and, one presumes, subcutaneously), in which case the rate of absorption is a function of the concentration of the sugar. Cori's results suggest that the presence of other sugars would diminish the rate of absorption of dextrose from the intestine. If this is true, dextrose theoretically should not be mixed with other sugars when the most rapid absorption is desired. From a practical point of view the difference of rate is probably of little significance in most cases. When the sugar is absorbed it passes first, of course, to the liver, where glycogen may be formed. Endogenous insulin also passes first to the liver. The glycogenic and other functions of the liver may be facilitated during digestion by an accumulation of blood in this organ produced by constriction of the hepatic veins and dilatation of the

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portal system. The recent results of Bauer, Dale, Poulsson and Richards (1932) suggest the possibility that vasodilator materials either absorbed from the intestine, or perhaps produced in the liver, may be responsible, in some species, for this accumulation of blood. It is interesting that the liberation of adrenalin which, for example, might accompany strenuous muscular exercise or excitement, would probably produce a dilatation of the hepatic veins with the resulting emptying of the accumulated blood from the liver, and perhaps an interference with hepatic function. The rise in blood sugar which accompanies the absorption of carbohydrate elicits an increased liberation of insulin from the islet cells. The exact mechanism of action of the sugar is still debatable, but if we accept the experimental results of La Barre and Zunz (1927, 1929, 1930) evidence would be available that the sugar acts by stimulation of the parasympathetic centers in the hypothalamic region of the brain. The sugar is said to produce no effect after section of the vagus nerve, or paralysis of the vagus endings in the pancreas, by the use of atropine. From a morphological point of view we would expect the right vagus nerve to exert some effect on the islet cells, since this nerve sends fibers to the pancreas, which are distributed in close proximity to and may even pierce the accumulations of islet tissue. We cannot accept, however, at the present time, the conception that sugar must always act by the stimulation of vagus endings until some further evidence is secured that there are functioning vagus endings in an apparently denervated pancreatic remnant. On the other hand, it is certainly not established that this pancreatic remnant permits normal glucose tolerance, and that it does not merely liberate more or less continuously a very small amount of insulin. Unfortunately at present we have no method of measuring exactly the insulin content of blood, but it has been satisfactorily established by physiological procedures that the output of insulin from the pancreatic vein is definitely augmented when the concentration of the sugar in the blood is raised. It would seem, therefore, that if it is desired to decrease the strain upon islet tissue some consideration should be given to the level of blood sugar throughout the twenty-four hours, with a view to determining the length of time during which this is above the normal figure. One may suppose that the longer the period the level is above the normal, the greater the stimulation of the islands of Langerhans. We have no data which enable us to decide whether or not the intensity of stimulation is proportional to the level of hyperglycemia. However, one might expect that 50 grams of ingested sugar would cause much greater stimulation of insulin liberation than the amount of protein which would enable 50 grams of sugar to be manufactured over a period of time within the body. If the formation of sugar from fat takes place, it is probably a gradual process. There are grounds for believing that one of the explanations of the apparently beneficial effect of very high carbohydrate diets may be the liberation of insulin. If the diet continues to be satisfactory for long periods the stimulation of islet cells may, of course, be considered harmless. In some cases when carbohydrate in excess of that pro-

vided in the adequate diet for a normal person is allowed, the beneficial effect does not persist. Now, there is satisfactory evidence that the insulin which is liberated from the islet cells not only increases glycogen formation in the liver, but also inhibits the new formation of sugar from protein, and probably from fat, in that organ. Contrary to the frequently quoted view, accumulation of glycogen in the liver may take place even though there is an abundance of fat present, and vice versa. There are numerous reports in the clinical literature and some experimental evidence to suggest that a glycogen-rich liver is able to function better and to resist deleterious influences to a greater degree than one which is poor in glycogen. It is easy to demonstrate in diabetic animals that excessive fat deposition in the liver is accompanied by profound interference with sugar formation and other hepatic functions. We have found it possible to decrease glyconeogenesis in diabetic animals to such an extent by adding fat to the diet that the blood sugar sinks to within the limits found in normal animals. The liver becomes intensely fatty and the animal may die suddenly. The point I wish to make here is that apparently beneficial effects may be produced in the diabetic by procedures which are fundamentally injurious.

Now, of course, liver glycogen formation does not account for nearly all the sugar which disappears under the action of insulin. Accumulation of this carbohydrate reserve in muscle is also easy to demonstrate. The evidence at present strongly suggests that insulin is not, however, necessary for the formation of small amounts of glycogen in muscle (Cori, 1929, and Major and Mann, 1932). There can be no doubt, however, that insulin greatly increases the rate at which sugar is converted into glycogen in muscles and, indeed, under some conditions in experimental animals insulin is the deciding factor. It has been stated by Hoet and his co-workers (1931) that glycogen broken down by muscular contraction is not resynthesized in muscle after the vagi are cut. In other words, it is thought that the liberation of insulin from the pancreas is absolutely necessary for the resynthesis of glycogen under these conditions. It appears probable from the work of Long and Horsfall (1932) that the formation of glycogen from glucose under the action of insulin favors the formation of glycogen from lactic acid, i.e. favors the recovery of muscle from exercise. There is evidence that there is accumulation of muscle glycogen during some phases of the change in muscle which accompanies physical training. All these points emphasize the importance of insulin in muscle metabolism and excite our curiosity concerning the magnitude of the disturbance produced when there is not complete absence, but only an insufficiency of insulin production, or a partial inactivation of available insulin by the products of infection, such as may occur in many clinical cases. These findings are of considerable interest also in the interpretation of the beneficial results which follow intravenous glucose in so many clinical conditions. The glucose solution, in addition to supplying fuel and water, would liberate insulin and cause or facilitate the changes in liver and muscle which I have described.

If I were able to add much to the obvious facts concerning the effects of infection on carbohydrate tolerance I would discuss the subject fully. Experimentally it can be shown that liberation of adrenalin and possibly thyroxin is one of the effects of the products of bacterial action. Quite recently Murray and Waters (1932) have shown that the insulin content of the pancreas is lowered in infected animals. This does not necessarily mean that the rate of liberation from the pancreas is reduced, but the result encourages us in the attempt to determine whether or not this is the case.

Increased oxidation of carbohydrate in diabetic animals undoubtedly accounts for a part of the sugar which disappears under the influence of insulin. A great deal of experimental evidence establishes the fact that the oxidation of carbohydrate is not in abeyance even in the completely depancreatized animal (Soskin, 1931).

We know that the fatty acid content of blood and tissues of diabetic animals can be decreased by insulin administration. The ketone bodies are, of course, brought to within normal limits by the appropriate use of this substance. Instead of discussing in further detail these well-known effects of insulin on fat metabolism, I will spend what time remains to me in describing the present position of a certain problem in fat metabolism which happens to be my own major research interest at the moment.

The research which I am going to discuss deals in large part with the health of the members of a colony of diabetic dogs which have been observed continuously in the Department of Physiology since 1921. The original members of this colony were, of course, those upon which the experiments leading to the isolation of insulin were conducted. These diabetic animals were our only test subjects until Collip's studies on normal rabbits made that species available. The rise in oxygen consumption and in the respiratory quotient of a diabetic animal when insulin and sugar were given (observed by Hepburn and myself) provided the first evidence that the combustion of carbohydrate was actually increased by the administration of insulin. Storage of liver glycogen and lowering of liver fat by insulin were first demonstrated in these diabetic dogs. The excretion of ketone bodies in these animals was definitely reduced by the administration of insulin. Symptoms of insulin hypoglycemia were observed and described in the diabetic dog but were not attributed to the low blood sugar until after studies on rabbits had been conducted. The glucose equivalent of insulin was carefully determined in depancreatized animals by Allan (1924), who found that when the carbohydrate ingestion was constant the glucose equivalent per unit became progressively smaller as the dose was increased. When the *amount of* insulin was kept constant and the carbohydrate was increased, the glucose equivalent of the insulin rises up to a certain point and from then on is practically constant. This finding accounts in part for the favorable results obtained clinically with diets higher in carbohydrate. The interrelationship of phosphate and carbohydrate in the metabolism of diabetic animals was investigated by Sokhey and Allan (1924) and by Markowitz

(1926). A great variety of anti-diabetic substances have been tested on these diabetic dogs. It is possible to control the diet of the animals accurately and to eliminate subjective effects completely. For these reasons the diabetic animal is perhaps the most suitable subject for the investigation of the anti-diabetic action of any material. Intarvin, synthalin, various extracts from plant sources, liver fractions and so on have been tested, and in the cases mentioned no evidence of any therapeutic effect was secured. It has been found possible to keep these diabetic animals alive for what may be considered an indefinite time. The dog which Banting and I observed for 70 days could undoubtedly have been kept in good condition for a much longer period of time, but we wished to verify the completeness of the pancreatectomy. We observed no abnormal signs in the animal which insulin failed to alleviate. In later experiments, however, Allan, Bowie, Macleod and Robinson (1924) found that depancreatized dogs receiving sufficient insulin and a lean meat and sugar diet, did not keep in good condition indefinitely, but this could be achieved when the diet included raw pancreas. These observers could not, of course, be certain of the mechanism of action of the raw pancreas. Since the characteristic pathological finding in the animals was a fatty infiltration and degeneration of the liver, they debated the possibility that the effect of the raw pancreas might be due to the provision of lipase, in the absence of which fat liberation might have been deleteriously affected. The idea that toxic products may have been formed from undigested protein in the intestine was also considered. While the possibility was mentioned that some chemical substance necessary for the proper metabolism of fat might have been supplied in the minced pancreas, no experiments to investigate this were conducted at that time. Inspired by Leathes' theories concerning the significance of lecithin in fat metabolism, Hershey (1931) tried the effects of adding crude lecithin to the diet of these animals, with most interesting results. To make a long story short, I believe that sufficient evidence has now been accumulated to show that lecithin is able to prevent the development of fatty livers in these animals. Furthermore, we have found that the onset of the fatty condition can be accelerated by adding fat to the diet. In experiments on normal rats, Miss Huntsman, Mr. Hershey and I (1932) have obtained evidence that the active constituent of the lecithin is choline. In several instances Ferguson, Hershey and I have obtained evidence that choline will prevent or modify the fatty changes in the livers of depancreatized dogs, but we still have a great deal to learn concerning this matter. We are at present investigating the rôle of choline in fat metabolism in two series of experiments on these dogs. In the first series we are producing fatty livers by withholding any source of choline. A small lobe of liver is then removed for analysis and histological study. If the liver is very fatty, choline is supplied, and the second operation is done when choline has been given an opportunity to produce its effect. As I have said, the results thus far obtained would indicate very definitely that choline is preventing fatty changes in the livers of these animals. In the

second series of experiments we are studying the effect of choline upon fat tolerance curves, but cannot predict what the results of this investigation will be. I will just pause here to mention that surprisingly little is known about fat tolerance and that the field is well worth further exploration both clinically and in experimental animals. In conclusion it is important to note that the fatty changes in the livers of normal rats can be prevented by an oxidation product of choline, betaine, which has no pharmacological properties (Best and Huntsman, 1932). Furthermore, fatty changes in the livers of rats produced by cholesterol can be inhibited by choline (Ridout and Best).

Experiments with diabetic dogs are tedious, and the assistance of patient collaborators and technical assistants is indispensable. I may say, however, that when a clear-cut experimental result is obtained, one feels as a result of previous experience that it can be applied with much more assurance to the treatment of the human diabetic than results obtained in normal animals of the same or of other species.

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THE ANALYSIS OF HIGH CALORIC DIETS IN RELATION TO WEIGHT CHANGES*

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For a period of four years, we have studied the treatment by dietary measures of patients who were underweight. The principles underlying this treatment and the clinical results have been summarized in a previous paper.[6] Eighteen patients were studied on the metabolic pavilion of the Western Pennsylvania Hospital for periods varying from two to 13 weeks. On 16 subjects of this series the detailed data of the food taken in are sufficiently complete to permit analysis. The analysis of these diets with reference to the weight changes which were observed forms the subject of this present study.

Methods

The methods for the estimation of food intake were the standardized procedures which have been in use for several years. For these special study patients, all food was weighed on a balance to the nearest .1 gram. Food which was returned was reweighed and subtracted from the initial value. The menus for these patients consisted of only the simple foods, served in a simple manner in order to facilitate the accurate estimation of food eaten but more especially of food returned. Water was supplied in any desired amounts from weighed bottles which were provided with two-holed rubber stoppers through which appropriate glass tubes passed. The figures for the analyses of the several foods were taken for the most part from Atwater and Bryant,[1] Sherman,[5] Waller,[8] Friedenwald and Ruhrah [3] and a few analyses of our own (unpublished). No group analyses were used.

In construction of the diets of this series, due care was taken to supply ample quantities of the various accessory food substances. No details are available but it is felt that all possible needs were liberally supplied. Many of these patients received medication for some time during their stay. Strict account was kept of all medicines used. The total weight taken and the estimated caloric values of the drugs and more particularly of their vehicles were noted. In most cases the calories thus provided formed an insignificant portion of the average intakes. One patient, however, obtained 30 calories per day from this source.

The figures which appear in the tables are the averages for the entire periods of observation of the individual patients. Although six patients were observed for only two to three weeks, six patients stayed for six weeks

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or more. The average length of stay was 5.4 weeks. It was, of course, impossible for persons to eat exactly the same daily intake over these long periods. Considerable variation was noted from day to day. These variations were most marked in patients who were subjected to diagnostic procedures such as cystoscopic examinations. Intercurrent infections also required temporary departures from the desired routine. Such fluctuations in intake are reflected temporarily in body weight. For example, patient 1 took in only 608 calories on one day and lost 700 grams of weight in this same period. It should, however, be recognized that shifts in water balance are chiefly responsible for these daily weight fluctuations.

Body weight observations were made under standard conditions at 7 a.m. daily. In order to minimize the numerical influence of water shifts, the initial and final weights which are recorded in the tables represent the respective average weights of the day before, day of, and day after the designated date. However, even with these precautions, the short experiments are undoubtedly much more affected by water shifts than the longer studies, as indicated by the marked deviations of the figures for weight gain per 100 extra calories of patients 3 and 14 who were observed for only three weeks. (Table 8, Column 8.)

Observations

The analysis of the average figures for the food eaten by these patients appears in detail in table 1. The 16 patients averaged 3320 $\pm$ 500 calories

Table I

Average Composition of High Caloric Diets

1	2	3	4	5	6	7	8	9	10	11	12
Patient	Total calories	Protein			Carbohydrate			Fat			FA/G
		Gm.	Cal.	% Total Cal.	Gm.	Cal.	% Total Cal.	Gm.	Cal.	% Total Cal.	
1	2790	42.8	171	6.1	248	992	35.6	175	1627	58.3	.61
2	2310	56.0	224	9.6	211	844	36.5	134	1246	53.9	.57
3	2850	53.0	212	7.4	228	912	32.9	186	1729	60.5	.69
4	3200	62.3	250	7.8	275	1100	34.4	199	1851	57.8	.63
5	2980	57.8	231	7.7	51	204	6.8	274	2549	85.5	2.44
6	5090	115.5	462	9.0	399	1596	31.4	326	3033	59.6	.69
7	3280	74.9	300	9.1	286	1144	34.9	197	1832	55.9	.61
9	3430	70.5	282	8.2	284	1136	33.1	217	2018	58.7	.65
10	3200	55.8	223	6.9	219	876	27.4	226	2102	65.7	.83
12	3310	47.0	188	5.7	79	316	9.5	302	2808	84.8	2.14
13	3450	45.7	183	5.3	41	164	4.8	333	3096	89.9	3.17
14	3060	70.0	280	9.1	241	964	31.5	195	1814	59.2	.67
15	3260	55.6	222	6.8	253	1012	30.9	219	2037	62.3	.73
16	3310	62.5	250	7.5	226	904	27.3	232	2158	65.1	.83
17	2800	76.3	305	10.7	229	916	32.7	170	1585	56.6	.65
18	4790	87.9	352	7.4	371	1484	31.0	317	2949	61.6	.72
Average	3320	64.6	258	7.7	228	910	27.5	231	2152	64.7	1.04

per day. This figure includes the two patients, 6 and 18, who maintained the phenomenal intakes of 5090 and 4790 calories per day for six and seven weeks respectively. If these two extraordinary cases are omitted, the average of the 14 more ordinary subjects is 3090 $\pm$ 250 calories per day.

The distribution of this food intake into the three principal groups shows great case variation. The protein intake was, however, rather uniform. Most of the patients were ordered 1 gram protein per kilogram ideal weight. The average intake was 65 grams which provided 7.7 per cent of the total calories. The individual intakes varied from 43 to 116 grams while the percentage of total calories varied from 5.3 to 10.7 per cent. In this connection it may be mentioned that roughly half of the protein intake was made up of animal proteins of high biological value.

The amount of carbohydrate in the diets averaged 228 grams which provided 27.5 per cent of the total calories. Three patients were placed upon low carbohydrate rations in which 40 to 80 grams per day were given. Although only 5 to 10 per cent of the total calories were provided by carbohydrate, these patients gained weight in a satisfactory manner. It may, however, be noted in table 3, column 13, and table 8, column 8, that the respective rates of weight change and the rates of change per 100 extra calories for these patients are among the lower values.

The fat content of high caloric diets must of necessity be high; 64.7 per cent of the calories were derived from fat although the actual average weight of fat was no greater than of carbohydrate. One patient received 90 per cent of her intake as fat, two others 85 per cent. The majority of patients, however, took between 55 to 65 per cent. It is of interest that the majority of patients ate slightly more carbohydrate than fat and that the two patients with exceptionally high total intakes, ate 50 to 60 grams more carbohydrate per day than fat.

The relative amounts of potentially ketogenic and anti-ketogenic substances in these fattening diets are of considerable interest. Three patients were given fatty-acid-glucose ratios of 2.14, 2.44, 3.17, respectively. These diets were adequately handled without observable ketosis. This observation is in accord with the experience which has developed during the reduction of obese patients, namely that normal cells will adapt themselves to handle any ratio of ketogenic to anti-ketogenic substances which may be brought to them. The average ratio for the entire group was 1.04. If, however, we consider the 13 patients whose ratios ranged from .57 to .83, it will be seen that the more ordinary diets had an average ratio of .68.

It might, a priori, be supposed that diets containing large quantities of concentrated foodstuffs might introduce large quantities of acid materials and burden the excretory system. Such, however, does not appear to be the case. The acid-base balance, of course, varies considerably with the exact items of food which are ingested. It is a profitless burden to determine the daily balance for the 600 days of study. Typical menus have been prepared for 2000, 3000, and 4000 calorie diets. The distribution of acid and base radicles is recorded in the usual terminology in table 2.

TABLE II

Acid-Base Balance of 2000, 3000, and 4000 Calorie Diets

1	2	3	4	5	6	7	8	9	10
Food	2000 Calories			3000 Calories			4000 Calories		
	Gms.	Excess acid c.c.	Excess base c.c.	Gms.	Excess acid c.c.	Excess base c.c.	Gms.	Excess acid c.c.	Excess base c.c.
Oatmeal	120	2.35		120	2.35		120	2.35	
Cream	100		.60	200		1.20	400		2.40
Egg	50			50			50		
Bread	90	6.07		120	8.10		140	9.45	
Butter	29			106			127		
Orange	125		7.01	150		8.41			
Apricots	120		8.16	150		10.20	200		13.60
Pears	125		4.50	150		5.40			
Potato	200		13.60	200		13.60	200		13.60
Asparagus	100		.81	100		.81	100		.81
Celery	50		3.89	50		3.89	50		3.89
Tomato	50		2.80	50		2.80	50		2.80
Cauliflower	100		5.33	100		5.33	100		5.33
Carrots	100		10.80	100		10.80	100		10.80
Peas	100		1.30	100		1.30	100		1.30
Sirloin	90	11.26		60	7.50		45	5.63	
Roast veal	90	12.16		65	8.78		45	6.08	
Sugar	20			40			60		
Bacon				30	1.60		40	2.08	
Banana							150		8.34
Cherries							150		6.60
Total		31.84	58.80		28.33	63.74		25.59	69.47
Balance			26.96			35.41			43.88

It is noteworthy that in this series of diets the amount of base is roughly twice that of the acid. Also the proportion of base increases with the increase in calories. It should, of course, be recognized that this phenomenon is dependent upon this particular selection of foods and is not necessarily applicable to other menus. It appears to be true, nevertheless, that in the vast majority of the high calorie diets which we have employed, the amount of base far exceeds the amount of acid.

It is of interest to note the bulk of food which was eaten by these patients in relation to the body weight and to the caloric value of the diet. The significant data for 14 patients are summarized in table 3.

The average total weight of average intake was 3176 grams (7 pounds) with a range from 2082 to 4860 grams. Intakes of these magnitudes form a very significant fraction of the total body weight. In fact, two patients had daily mass exchanges of 9.3 per cent and 9.5 per cent of their body weights respectively although the average for the series was 6.9 per cent of the body weights. Of the total intake, 61 per cent was food and 39 per cent water. Considerable variation in the proportions of

TABLE III

Relation of Intake to Caloric Value and Weight Gains

1	2	3	4	5	6	7	8	9	10	11	12	13
Patient	Total intake		Food intake			Food solids			Calories per gram			Wt. Gain
	Weight	% Body weight	Weight	% Total intake	% Body weight	Weight	% Total intake	% Food intake	Total intake	Food intake	Food solids	Gms. per day
	Gm.	%	Gm.	%	%	Gm.	%	%	Cal.	Cal.	Cal.	Gm.
1	3345	7.0	1557	46	3.3	465	14	30	.83	1.79	5.99	121
2	2082	9.3	1748	84	8.0	401	19	23	1.11	1.32	5.76	83
3	3102	7.4	1678	54	4.0	466	15	28	.92	1.70	6.12	248
4	2853	6.3	1927	68	2.3	529	18	27	1.12	1.66	6.05	157
5	2994	5.7	1303	43	2.5	382	13	29	.99	2.29	7.80	114
6	4311	8.5	2521	58	5.0	841	19	33	1.18	2.02	6.05	421
7	3141	6.7	2283	73	4.8	558	17	24	1.04	1.43	5.88	143
9	3722	7.6	2405	65	4.9	563	15	23	.92	1.43	6.09	164
10	2408	5.1	1791	74	3.8	500	20	28	1.33	1.79	6.40	154
14	3953	7.5	2140	54	4.1	506	13	23	.77	1.43	6.05	257
15	3091	6.2	1765	57	3.5	527	17	29	1.05	1.85	6.18	177
16	2771	4.9	1728	62	3.0	521	19	30	1.19	1.92	6.36	178
17	2837	5.9	1766	62	3.6	475	17	24	.99	1.58	5.89	131
18	4860	9.5	2700	56	5.3	776	16	29	.99	1.77	6.17	186
Ave.	3176	6.9	1951	61	4.2	536	17	27	1.03	1.71	6.20	181

food and water are to be expected both in individuals and in the daily levels. For two patients, water formed 64 to 57 per cent of the total daily intake. In contrast, one patient drank only 16 per cent water. Conversely the weight of food varied from 43 to 84 per cent of the total intake. The food intakes ranged from 1300 to 2700 grams with an average of 1951 grams per day. These figures represent on the average 4.2 per cent of the respective body weights. Since the figures for food include the large quantities of water in the food substances, the total weights of the food solids have been estimated separately (column 7). It may be noted that 536 grams of solids were taken per day with a variation from 382 to 841 grams. The food solids correspond to 27 per cent of the total weight of food and to 17 per cent of the total weight of intake.

Since the foods taken, with a few exceptions, were general mixed varieties, it is important to note the relations which existed between total weight and energy content of the intake. As might be expected, the marked variability in extra water produces a great variation in the relation of total weight of intake to caloric value. Although the average figure is 1.03 calories per gram the extremes are 1.33 and .77 calories per gram. If the weight of only the food substances is considered the variability is obviously somewhat less, while the average value becomes 1.71 calories

per gram. If, however, only the food solids are considered, there is a fair degree of constancy, about the average value 6.20 calories per gram. The only marked variation occurred in patient 5 who ate a diet containing 85 per cent of fat which produced 7.80 calories per gram of solids.

An attempt has been made to correlate these data pertaining to food weights with the observed changes in body weight. Although the average daily weight gain (181 grams) corresponds to 5.6 per cent of the total weight of intake per day, there is, as would be expected, little individual correspondence between these two series of observations; also with respect to the total weight of food intake, or conversely the total weight of water intake, no clear cut relation to weight gain is apparent. Finally the average weight gain corresponds to 34 per cent of the weight of the food solids but here again an examination of the data fails to reveal a true relation between weight of intake and body weight gain. It may therefore be stated that a permanent gain in body weight bears no relation to the total mass of material, either food or water, which is ingested.

If we accept the principle that the truly significant aspect of a fattening diet is its caloric value, the relation of the weight changes of these patients to their caloric intakes becomes of great interest. From table 1 it will be seen that the average caloric intake for 16 patients was 3320 calories with a range from 2310 to 5090 calories. However, in proportion to the sizes of the individuals, the variation appears to be much less. From table 4, column 13, it may be seen that the average calories per kilogram of average weight is 73, with a range from 57 to 105 calories per kilogram. Attention may be called to the fact that the patient having only 2310 total calories actually averaged 105 calories per kilogram. Ratios of this order of magnitude serve to emphasize the point that the standards of 30 to 40 calories per kilogram which are often encountered certainly are inadequate when one is dealing with underweight patients. Our ratios compare rather with those of Coleman and DuBois [2] who found 50 to 70 calories per kilogram necessary to maintain the weights of typhoid patients. If, however, the calories per kilogram are calculated on the basis of the ideal weights of the patients much lower figures are obtained. In this series of patients who increased from 26 per cent underweight to 16 per cent underweight, the average intake was 57 calories per kilogram of ideal weight in contrast to the 73 calories per kilogram average actual weight.

It may be accepted as a fact that a food intake adequate for weight gain exceeds that for maintenance. In order to obtain a measure of how much thin people actually eat regardless of their impressions, preliminary observations were made on eight patients. These patients were instructed to eat just as they did at home or just as they wished, although in most cases it was impossible for them to avoid an increase in intake as shown by their weight gains. These results are tabulated in table 4.

The average food intake was only 2060 calories or roughly two-thirds of the corrective diet. In proportion to body size, these intakes average 52

TABLE IV

Preliminary Diet and Increase in Food Capacity

1	2	3	4	5	6	7	8	9	10	11	12	13	14
	Preliminary diet					First week		Final week			Average total cal.	Calories per kilo	
Pt.	No. days	Ave. body wt.	Calories	Protein	Calories per kilo	Calories	Cal. per kilo Initial wt.	Wk.	Calories	Cal. per kilo Final wt.		Ave. wt.	Ideal wt.
1						2440	58	14	2840	53	2790	59	47
2	4	20.9	1880	52	90	2290	108	3	2160	95	2310	105	80
3	5	38.6	1670	32	46	2280	59	3	3190	70	2850	69	50
4	3	43.2	2270	73	52	2630	61	4	3500	74	3200	71	59
5						2730	55	6	3090	57	2980	57	46
6						4860	117	6	5320	90	5090	101	72
7						2540	62	12	3510	66	3280	70	59
8	3	44.0	1850	49	42	2160	49	2	3103	68			
9						3400	72	2	3460	69	3430	70	56
10						3110	70	4	3200	65	3200	68	53
12						3570	101	8	3370	80	3310	85	57
13	7	39.7	2220	47	55	3290	83	3	3540	82	3450	83	60
14						3060	62	3	3050	55	3060	59	52
15	2	45.7	2340	52	51	3610	77	5	3380	64	3260	66	52
16	7	54.0	2450	60	45	2970	55	4	3470	59	3310	58	52
17	5	46.0	1770	62	38	2570	55	3	2910	59	2800	58	49
18						3710	80	7	4460	80	4790	94	72
Ave.						3010	. 72	5	3380	70	3320	73	57
Ave. Preliminary diet group	4		2060	53	52	2730	68	3	3160	71			

calories per kilogram actual weight. In contrast it may be noted that these patients took in 68 to 71 calories per kilogram of average actual weight during the period of treatment. These data show that according to certain standards, thin people do eat large quantities of food but again it may be stressed that the total caloric intake is small in these persons.

The increase in the food capacity of our patients is shown in table 4, columns 7 to 11. Columns 8 and 11 record the calories per kilogram of actual weight eaten during the first and last weeks. It at once appears that there is little difference between these figures. The apparent discrepancy is due to the increase in final weight rather than to a lessened intake. When the total calories taken during the first and last weeks are compared it will be noted that patients ate 400 more calories or 13 per cent more food than during the first week. As a matter of fact this maximum intake was attained usually in the second or third week, an observation which supports our practice of starting a patient at once on a full diet or, at most, of making one or two steps at short intervals. A comparison of the figures for the first week with those for the preliminary period shows that the patients who ate 2060 calories for maintenance averaged 2730 calories during the first week and reached 3160 calories in the last week of dieting. These increases are 32 and 53 per cent respectively. No significant difference in reaction could be noted in the patients having acute undernutrition as contrasted with chronic undernutrition.

The changes in weight which have been produced by the above diets are recorded in table 5.

TABLE V

Weight Increase

1	2	3	4	5	6	7	8	9
Patient	Weeks	Initial weight		Final weight		Increase weight		Rate of increase Grams per day
		Kilo	% Under weight	Kilo	% Under weight	Kilo	%	
1	13½	41.9	30	53.3	11	11.4	27	121
2	3	21.2	27	22.9	21	1.7	8	83
3	3	38.9	31	44.1	22	5.2	13	248
4	4	43.1	20	47.5	12	4.4	10	157
5	6	49.5	23	54.3	16	4.8	9	114
6	6	41.4	42	59.1	17	17.7	43	421
7	12	40.9	25	52.9	3	12.0	29	143
8	2	44.0	19	45.7	15	1.7	4	121
9	2	47.6	20	49.9	18	2.3	5	164
10	4	44.6	26	48.9	18	4.3	10	154
11	3	34.7	28	36.9	23	2.2	6	102
12	8	35.1	40	42.2	28	7.1	20	127
13	3	39.5	32	43.0	26	3.5	9	166
14	3	49.9	15	54.8	6	5.4	11	257
15	5	46.6	25	52.8	16	6.2	14	177
16	4	54.1	13	59.0	6	4.9	9	178
17	2½	46.7	18	49.0	14	2.3	5	131
18	7	46.4	30	55.5	17	9.1	19	186
Average	5	42.5	26	48.4	16	5.9	13	169

The 18 patients forming the entire series gained 106.2 kilograms, an average of 5.9 kilograms per person. The largest individual gain was 17.7 kilograms in six weeks, the smallest 1.7 kilograms in three weeks. The average increase in weight per day was 169 grams, with a range from 83 to 421 grams per day.

It is further of interest to note the relation of the weight increments to the body status which had existed previously. The patients increased their body mass on the average by 13 per cent varying from 4 per cent in two weeks to 43 per cent in six weeks. On the whole they changed stature at the rate of 2.8 per cent per week.

The six patients who were more than 30 per cent underweight appear to have gained 35 per cent more rapidly than the 10 who were less than 30 per cent underweight, 211 grams per day as contrasted with 156 grams per day (table 6).

TABLE VI

Weight Gain in Relation to Degree of Undernutrition

Less than 30 per cent					More than 30 per cent				
Patient	Wt. gain per day	Caloric intake	Calories per kilo	Wt. gain per 100 extra cal.	Patient	Wt. gain per day	Caloric intake	Calories per kilo	Wt. gain per 100 extra cal.
	Gm.	Cal.	Cal.	Gm.		Gm.	Cal.	Cal.	Gm.
2	83	2310	105	15	1	121	2790	59	20
4	157	3200	71	13	3	248	2850	69	29
5	114	2980	57	13	6	421	5090	101	17
7	143	3280	70	12	12	127	3310	85	9
9	164	3430	70	11	13	166	3450	83	11
10	154	3200	68	13	18	186	4790	94	9
14	257	3060	59	28					
15	177	3260	66	17					
16	178	3310	58	17					
17	131	2800	58	18					
Ave.	156	3080	68	16	Ave.	211	3710	82	16

It would appear, therefore, as if the rate of weight gain might vary inversely with the degree of undernutrition. This phenomenon is, however, apparent only. Although the rate of weight gain of the six grossly undernourished patients was high, this may be explained readily on the higher caloric intake. These patients averaged 3710 calories per day in contrast to the 3080 for 10 other patients, or 82 calories per kilogram in contrast to 68 calories per kilogram. Further confirmation of this point is obtained by comparing the grams weight increase per 100 extra calories in the two groups. The six very low weight patients averaged 16 grams per 100 extra calories as compared with 16 grams for the other subjects.

Since it is obvious that the weight change bears a direct relation to the

increase in food intake, it becomes important to attempt a statement of this relationship. More strictly speaking, the relationship exists between the rate of weight gain and the excess of food intake. A discussion of this energy balance requires a knowledge not only of the intake but of the output of energy. The total daily energy output could not be determined. We have used, however, three methods of approximating this information. The preliminary diets may be regarded as representative of the maintenance intake and the excess calories estimated by difference between intake on the high caloric and on the maintenance diets minus the extra specific dynamic action of the dietary increase. This calculation for seven patients on whom preliminary diet data are available appears in table 7.

TABLE VII

Extra Calories Estimated from Preliminary Diet

1	2	3	4	5	6	7	8
Patient	Caloric intake	Maintenance calories	Gross extra calories	Increase S D A	Net extra calories	Weight gain per day	Weight gain per 100 extra cal.
	Cal.	Cal.	Cal.	Cal.	Cal.	Gm.	Gm.
2	2310	1880	430	40	390	83	21
3	2850	1670	1180	120	1060	248	23
4	3200	2270	930	90	840	157	19
13	3450	2220	1230	120	1110	166	15
15	3260	2340	920	90	830	177	21
16	3310	2450	860	90	770	178	23
17	2800	1770	1030	100	930	131	14
Ave.	3030	2090	940	90	850		19

It may be noted that these patients ingested 3030 calories per day in contrast to 2090 calories during the preliminary period. If we neglect the slight weight increase during the earlier period, 940 extra calories were eaten. The specific dynamic action of this extra food reduces the net extra calories to 850. If the respective daily weight gains are divided by the net extra calories it is found that these patients gained 19 grams per 100 extra calories eaten.

A second approximation of the total energy output is obtained by the arbitrary assumption that the extra basal heat production is 20 per cent of the basal level. The total heat output is, therefore: Basal + 20 per cent + specific dynamic action (10 per cent of the food intake). The details of this method are not given but the average for 16 patients is 13 grams per hundred extra calories.

The third method resembles the second except for the arbitrary assumption of 500 calories as the extra basal heat output. The energy output is, therefore: Basal + 500 calories + specific dynamic action (10 per cent of

intake). The application of this calculation to the data of 16 patients appears in table 8.

The gross intake of the 16 patients averaged 3320. The average figure obtained by adding the observed 24 hour basal metabolism, 10 per cent of the gross food intake for specific dynamic action, and 500 extra basal calories is

TABLE VIII

Extra Calories Estimated from Basal Metabolism

1	2	3	4	5	6	7	8
Patient	Caloric intake	Caloric output			Extra calories	Weight gain per day	Weight gain per 100 extra cal.
		Basal	SDA	Total			
	Cal.	Cal.	Cal.	Cal.	Cal.	Gm.	Gm.
1	2790	1400	280	2180	610	121	20
2	2310	1020	230	1750	560	83	15
3	2850	1200	290	1990	860	248	29
4	3200	1190	320	2010	1190	157	13
5	2980	1280	300	2080	900	114	13
6	5090	1670	510	2680	2410	421	17
7	3280	1300	330	2130	1150	143	12
9	3430	1150	340	1990	1440	164	11
10	3200	1170	320	1990	1210	154	13
12	3310	1080	330	1910	1400	127	9
13	3450	1070	350	1920	1530	166	11
14	3060	1350	310	2160	900	257	28
15	3260	1410	330	2240	1020	177	17
16	3310	1410	330	2240	1070	178	17
17	2800	1310	280	2090	710	131	18
18	4790	1830	480	2810	1980	186	9
Ave.	3320			2140	1180		16

Nitrogen storage figures were available on only ten of these patients. If the weight gain per day for these patients is distributed into protein and fat, it will be found that the average weight of fat deposited per 100 extra, non-protein calories is 11.7 grams. This figure may be compared with the theoretical 12.6 grams of fat tissue per 100 extra fat calories.

2140. The net extra calories eaten are, therefore, 1180. The average of the respective weight gains divided by the extra calories is 16 grams per 100 extra calories.

Since in all probability no one of these methods of estimation exactly expresses the facts in any given patient, the most reasonable estimate is obtained by averaging the results of the three methods. The average figure, 16 grams per 100 extra calories, may be regarded as fairly representative of the rates at which our patients were observed to gain weight. This mode of expression, in our opinion, provides a more accurate picture of the intrinsic metabolic phenomena of weight gain than any other form of expression. The expression of weight changes in terms of total gain or of grams weight gain per day indicates the end results which have been ob-

tained. The mechanism by which these results are obtained is suggested by our observation of a fair degree of uniformity of the figures for weight change per 100 extra calories which is often in marked contrast to an apparently slow or rapid alteration in weight.

Further emphasis regarding the fundamental significance of these data is obtained by comparing the observed figures for grams weight gain per 100 extra calories with what is theoretically probable. In the estimation of the weight increase which might be expected from each extra 100 calories, it is necessary to keep in mind the nature of the tissues deposited. Mitchell and Carman [4] have shown the great variations in the several tissues which occur in animals on very similar diets. Also the great variation in water content of tissues is well known. However, admitting the inherent inaccuracies of the calculation, an approximation has been made on the assumption that the tissues deposited were protein and fat containing 75 per cent and 15 per cent water respectively.

Ten of the 16 patients had an average positive nitrogen balance of 2.3 grams.[7] It is, therefore, assumed that 2.0 grams nitrogen were stored by the average patient. If we refer to the three calculations above, the 2 grams of nitrogen were stored simultaneously with 900, 1200 or 1400 calories respectively. In each instance 2 grams of nitrogen correspond to 50 calories and to 50 grams of protein tissue. The fatty tissue estimates which correspond to the above total calories would be 107, 145, and 170 grams respectively. Per 100 extra calories, therefore, the theoretical weight gain in each instance would be 17.4, 16.3, 15.7 grams respectively with the average of 16 grams per 100 extra calories. In view of the several assumptions which have been made, too much stress should not be laid upon the coincidence of this close approximation of the observed and the theoretical weight gains. It is felt, however, that an agreement of this order provides considerable evidence in favor of the thesis that weight gain is regulated by the maintenance of an energy intake in excess of energy output and the rate of gain is determined by the magnitude of this excess intake.

Conclusions

1. An analysis of the diets taken by 16 patients who were being treated for undernutrition showed an average caloric intake of 3320 calories per day.

2. 7.7 per cent of the calories were supplied by protein, 27.5 per cent by carbohydrate and 64.7 per cent by fat.

3. The majority of the diets had ketogenic and anti-ketogenic ratios of .57 to .83, although the upper limit which was used was 3.17.

4. The estimation of the acid-base balance of the diets suggests that the average menus supplied a marked preponderance of basic radicles.

5. The total weight of intake averaged 3180 grams per day of which 61 per cent was food and 17 per cent food solids. No relation was observed between the weights of several intakes and the rate of weight gain.

6. The caloric intakes which were necessary for rapid weight gain averaged 73 calories per kilogram of actual weight or 57 calories per kilogram of ideal weight.

7. Thin people eat small quantities of food per day in spite of the apparent high levels which result from certain forms of calculation.

8. The food capacity of patients altered readily to permit the ingestion of 30 to 50 per cent increases of food intake.

9. Eighteen patients gained 106.2 kilograms in five weeks. The average rate of weight gain was .169 kilograms per day.

10. Dependent upon an approximation of the total caloric output, the extra calories ingested per day have been calculated. The rates of weight gain which were observed averaged 16 grams increase in body weight per 100 extra calories. This observed value is within reasonable agreement with the corresponding theoretical value.

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THE RHEUMATIC LUNG *

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The appreciation that the rheumatic virus may in certain cases attack both lung and pleura dates back almost two hundred years. Thus Boerhaave,[1] in 1737, stated that rheumatism invades "sometimes the brain, lungs and bowels." Störck [2] in 1762 also recognized the pleurisy of rheumatism. Maximillian Stoll [3] in 1788 was, however, the first to speak of "rheumatic pleurisy" and "rheumatic peripneumonia," but like Boerhaave gave no pathological description of these lesions. Chomel [4] in 1813 spoke with great caution of the inflammation of the pleura or lung which follows rheumatism. Latham [5] in 1845 and Fuller [6] in 1854 fearlessly championed the conception of a rheumatic pneumonia. Latham reported an incidence, of pulmonary affections in 136 cases of rheumatic fever, of 17.0 per cent. Fuller's series of 241 cases of acute rheumatism revealed pulmonary lesions in 41 cases or 17 per cent; these like Latham's figures were clinical observations. However, Fuller also reported 16 postmortems in which a pneumonia was found only twice, pleurisy five times, and bronchitis once. This discrepancy between clinical and postmortem incidence, I fear, still holds true today. In an excellent article by my father, the late R. P. Howard [7] in Pepper's *System of Medicine* in 1885, a good deal of space is devoted to the incidence of rheumatic pleurisy and pneumonia. According to this article, pulmonary and pleural manifestations occurred,

in rheumatic endocarditis in only 10.5 per cent
in rheumatic pericarditis in 58 per cent
in rheumatic endopericarditis in 71 per cent,

figures which are suggestive in themselves.

Cheadle [9] in 1889 also speaks of a pleurisy in rheumatic fever which may occur in two distinct ways. First it appears frequently toward the end of rheumatic heart disease, partly as a result of mechanical congestion of the pleura caused by the valvular defect or by pericarditis or by extension from the latter. Secondly as an initial phenomenon, preceding, accompanying, or immediately following the arthritis. Cheadle even suggests that it may occur quite independently of all other rheumatic infections. He reports two cases of pleuropneumonia in children but without postmortem confirmation.

Steven Mackenzie,[8] in a later contribution, found that among 3433 cases of rheumatic fever, pleurisy or pneumonia occurred in 9.94 per cent. In Germany, according to Pribram [11] in 1899, among 627 cases of rheumatic fever, there were four with a pneumonia; three of these were associated with endopericarditis and one with endocarditis alone; three had a pleurisy in addition. Only one case was studied post mortem and in it there was a

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bilateral lobular pneumonia. In other words, Pribram found an incidence in this German series of 0.64 per cent as compared with an average incidence, according to the British reports, of 1.52 per cent.

In 1903 Thomas McCrae [12] reported from the Johns Hopkins Hospital, four pulmonary complications among 270 rheumatic fever patients, an incidence of 1.5 per cent; three of these were pleurisy and one a pneumonia.

Rheumatic Pleurisy

According to Homer Swift,[13] in his article in Nelson's Loose-Leaf Medicine, 1920, the incidence of pleurisy is variously reported as from 2 to 20 per cent. W. S. Thayer [14] found in a series of 25 postmortems on acute rheumatic heart disease, a sero-fibrinous pleurisy in 10 cases (40 per cent) and a chronic adhesive pleurisy once. In a study by the writer and Dr. E. S. Mills,[15] of 241 cases of rheumatic fever or its sequellae occurring in a three year period (1925–1927 inclusive), there were seven cases of pleurisy among the 96 cases in the acute arthritic stage (an incidence of 7.3 per cent) and 20 cases in association with 130 cases of endocarditis, pericarditis, chorea or other rheumatic manifestations (an incidence of 13.3 per cent). The seven cases in the acute arthritic stage were sero-fibrinous and of these, three were bilateral, two right-sided, and two left-sided. Among the 20 cases in the other group, five were acute sero-fibrinous and 15 were chronic adhesive or obliterative pleuritis. In short, in 226 individual patients there was a pleurisy of some type in 27, an incidence of 11.9 per cent. There was an acute fibrinous pleurisy in four, sero-fibrinous in 12 and a chronic fibrous or obliterative pleurisy in eleven. It was right-sided in seven, left-sided in 10 and bilateral in 10 cases.

It is generally agreed that pleurisy is, next to carditis, the most common complication of rheumatic fever. Our conception of rheumatic pleurisy is that of a specific inflammatory lesion, similar to that of a rheumatic pericarditis or arthritis. Although this view has long been accepted, no definite description or characteristic pathological picture appeared in the earlier writings. It is true that in 1882 Longstreth,[16] of the Pennsylvania Hospital, emphasized the marked fibrinous character of the exudate and that Bezancon and Weil [17] in 1926 recorded the predominance of endothelial cells in the exudate. It was not, however, until 1928 that Paul [18] first described the specific nature of the pleurisy. On close inspection there is a thin film of fibrin on the surface of the pleura in the earliest stage, which may be replaced later by a thick fibrinous exudate on both parietal and visceral pleurae. Subsequently organization of the fibrinous adhesions occurs. Paul never found, however, the thickened hyalinized pleura seen so frequently in the late stages of tuberculosis.

Histologically the lesion resembles that seen in rheumatic pericarditis. " It is characterized primarily by changes in the pleural endothelium causing metaplasia and eventual death and desquamation of the endothelial cells. This is accompanied by a characteristic type of severe, chronic, non-suppura-

tive inflammatory reaction throughout the subpleural layers." Paul makes no mention of any structure remotely resembling the Aschoff body. This specific form of pleuritis is undoubtedly a common manifestation of the serous membrane involvement of the active stages of the disease and it is much more frequent than the pulmonary lesion proper. We agree with Gouley and Eiman [30] that it was often responsible for the diagnosis of so-called rheumatic pneumonia by the earlier students of the disease, as Latham and Fuller, who interpreted the physical signs of compression of the lung parenchyma by the pleural exudate as pneumonia and consequently reported an unusually high incidence of the latter. A pleurisy is found in the majority of cases that come to autopsy in either the acute or the subacute stage of rheumatic fever. It may be most extensive when complicating a widespread mediastinitis and pericarditis and is then usually associated with an effusion. However, it may exist in small isolated patches of fibrinous exudate seen more commonly over the lower lobes but at times also over the upper ones. Such small patches, of course, are not recognizable by any method of physical examination.

Rolly's [19] series of 3620 cases of acute rheumatic fever yielded 88 cases of pleurisy, or an incidence of 2.5 per cent, and in half of these the pericardium was also involved. While for many years the opinion had been expressed that the pericardium was first infected and the pleura only by direct extension, Paul concluded, in accord with the more recent conception of the widespread distribution of the rheumatic vascular lesions throughout the body, involving the peripheral arteries and arterioles, that the pleural lesions are part of the generalized process and not the result of a direct extension from the pericardium. Our pathologist, Dr. L. J. Rhea, has demonstrated in the pleura of one of our cases, Aschoff-like bodies.

Vascular Lesions

Since the description of Coombs,[20] Klotz,[21] and Pappenheimer and von Glahn [22] of the histological changes in the aorta in rheumatic fever, the peripheral blood vessels, including those of the lung, kidney, pancreas, colon, etc., have been also carefully studied. In a subsequent paper, von Glahn and Pappenheimer [23] reported that in the lungs of two of their cases practically every small branch of the pulmonary arteries was involved. Paul [24] found in one case typical Aschoff bodies in the adventitial layers of the pulmonary arteries as well as in those of the aorta. The gross and histological changes are not so striking in the pulmonary arteries of moderate size. In the small arterioles of the lungs, Paul found in from 20 to 40 per cent of the active rheumatic subjects a periarteritis in which all the coats were involved, though the intima and the adventitia were most affected. It is a striking fact, as pointed out by Paul, that in the vessels as in the pleura it is the endothelium which seems to be primarily involved and that this endothelial lesion is associated with a characteristic type of subendothelial perivascular and even interstitial reaction. Paul believes that there is a relationship be-

tween this type of lesion and the well known Aschoff body of the myocardium.

Rheumatic Pneumonia

No one will deny that a lobar pneumonia due to various types of pneumococci may occur during the course of rheumatic fever, but the question arises, is there a specific rheumatic pneumonia? Besnier (quoted by Garrod [25]) regarded the lesion in the lung as "splenization," and not a true exudative process but rather an intense hyperemia and edema with collapse and atelectasis. Coombs also considered atelectasis and passive congestion as responsible for the production of the pulmonary signs, but does admit of the possibility of a consolidation appearing in the right upper lobe, an area relatively immune to the influence of cardiac failure. Garrod has denied the existence of a specific pneumonia. Thayer found in 50 per cent of 25 fatal cases of rheumatic fever a terminal pneumonia or bronchopneumonia.

Rabinowitz [26] believed that a specific pneumopathy does occur and is clinically distinguishable from lobar as well as bronchopneumonia but that the ultimate proof of the existence of Aschoff bodies in the lung had not yet been produced. Paul found in the lungs of more than 50 per cent of 30 cases, "evidences of a focal hemorrhagic lesion, rather widespread, involving individual lobules or group of lobules, which might be interpreted as an early or hemorrhagic stage of a broncho- or lobular pneumonia." He, however, did not feel that sufficient evidence had been obtained to prove that this focal hemorrhagic lesion was a *specific* manifestation of rheumatic fever, although it seemed a fairly characteristic finding.

Naish [27] studied the consolidation in the lungs of six cases of rheumatic fever which had died at the height of the disease. He was struck in the first place with the extent of the pulmonary consolidation in four of the six cases, as nearly all of the five lobes were involved. Secondly, he emphasized the peculiar india-rubber like consistency of the affected lung: it was very tough and non-friable on section. The color too was striking, as the cut surface was of a purplish red shade, quite homogeneous, and showing none of the granite or marbled appearance of other pneumonias. Microscopically the most striking feature was the enormous endothelial proliferation, the cells apparently originating from the walls of the alveolar capillaries. Multinuclear cells were fairly frequent. These cells were mixed with a few fibroblasts and polymorphonuclear leukocytes. The reactive process appeared to be identical with that described by Aschoff and Tawara and Coombs as pathognomonic of rheumatic infection elsewhere in the body.

Coburn [28] found, among 3000 rheumatic subjects at the Presbyterian Hospital, New York, 30 patients in whom there suddenly developed pulmonary solidification accompanying active rheumatic disease without evidence of congestive heart failure.

The rapid disappearance and the migratory nature of these areas of consolidation were characteristic. He does not, however, describe anything characteristic in the postmortem appearance of the lungs other than

to mention as present, congestion, edema and a hyalinized membrane lying against the alveolar walls and some polymorphonuclear infiltration. He confesses that "the histological lesions regarded as specific in rheumatic disease have not been defined in the lung."

Eiman and Gouley,[29] as well as Naish, have described lesions in the lung that were eventually considered characteristic of the rheumatic virus, as seen elsewhere in the body. In an elaborate study in 1932 of nine fatal cases of acute rheumatic fever, Gouley and Eiman attempt to describe this specific pneumopathy. The inflammatory pulmonary reaction consisted of an interstitial exudate of large endothelial cells, identical in morphology with those found in the rheumatic heart lesions and generally considered pathognomonic of rheumatic fever. Hemorrhage and fibrinous exudate were prominent features. Both lungs were moderately enlarged and bulky and did not collapse: the lower lobes were solid and deep blue: on section the tissue was dark red in color and presented a cut surface of unusually smooth appearance and also a fairly dry one, giving a liver-like appearance resembling somewhat atelectasis. The histologic study revealed an acute interstitial inflammatory process, characterized by hyperemia, edema, and perivascular infiltration of large endothelioid cells, as well as multinuclear giant cells, plasma cells, lymphocytes and but relatively few polymorphonuclear leukocytes.

According to these writers, "The acute pulmonary lesion of rheumatic fever, rheumatic pneumonia, or pneumonitis, is an acute interstitial inflammation, having as its basis the vascular damage and perivascular infiltration that are common to all rheumatic lesions." "The rheumatic lesion's color, varying from dark blue to a rusty brown, and the delicate white tracing under the pleura, due to interstitial exudate, and its appearance on section are distinct features." "The dark red, firm, finely granular, slightly moist cut surface, doubtless led to its description as a splenization." Naish points out its resemblance to solid india-rubber." "It is not atelectasis." "Basal collapse, sometimes to an unusual degree and often accompanied by gelatinous edematous pleural adhesions, is seen frequently in subacute aspects of the disease." This consolidation could possibly be termed "perivascular pneumonia."

Histological examination gives definite proof of the identity of the lesion. The areas of acute involvement containing small perivascular groups of broken-up polymorphonuclears and slender irregular epithelioid cells might conceivably be the first of a number of phases of inflammatory reaction and be followed later by a non-proliferative process, the Aschoff "nodule." It is this interstitial perivascular infiltration of large cells, often multinucleated, that is a significant part of the histologic picture in rheumatic pneumonitis.

A third phase of the reaction is suggested by the presence of fairly large cells with solid irregular nuclei replacing the large Aschoff cells and giving the impression that such a lesion is a subacute one, verging on early sclerosis.

Another important feature is the vascular destruction that is usually seen in rheumatism, the endothelial hyperplasia, the rupture of capillaries with hemorrhage and the liberation of fibrin. Eight of the nine cases of Gouley and Eiman exhibited a pericarditis and all nine had some acute manifestations of cardiac rheumatism.

In the Montreal General Hospital during an eight year period a pneumonia was recognized clinically nine times in 489 rheumatic subjects; however, only two of these nine cases came to autopsy but in both the histological study was characteristic of a specific pneumonitis.

A clinical picture of lobar pneumonia may appear about the same time as the acute cardiac manifestations of rheumatic fever. However, it does not follow the presence of an upper respiratory infection as is usually the case in bronchopneumonia, nor does it present the striking features of the classical picture of lobar pneumonia, namely chill, high fever, rusty sputum, severe pleural pain, and tachypnea. Its symptoms are much less spectacular: there is no chill: cough may not be troublesome: the sputum is scanty and tenacious and only occasionally is it blood streaked: bacteriologically the sputum does not contain virulent pneumococci: as for the fever, it runs an irregular course, varying from 102 to 105 degrees and there is but a slight elevation of the respiratory rate.

The physical signs are much more striking than the symptoms. There may be dullness to percussion and bronchial breath sounds over the lower, or even over the upper lobes. But the striking feature is the transient character of the physical signs which may be present for only two to four days, though in some cases they may be prolonged to a week or more. The signs may recur in the same area in a few weeks.

The signs of consolidation may be replaced by flatness and absence of breath sounds due to a massive pulmonary collapse or to a pleural effusion, which may persist for weeks. There may be no râles present during the stage of consolidation or if present they are not as numerous or as intense as in the frank lobar pneumonia. In the later stage, large, coarse pleuritic râles may be heard due to the associated fibrinous pleurisy.

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TREATMENT OF POLYCYTHEMIA

THE RETICULOCYTE RESPONSE TO VENESECTION, PHENYLHYDRAZIN AND RADIATION *

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Venesection was formerly frequently employed as a therapeutic measure in the treatment of polycythemia, but its results have not been systematically studied. It has usually been considered as a measure of expediency rather than one of real value in the treatment of this condition. One of the present common objections to its use is based on the premise that repeated bleeding stimulates the bone marrow excessively, tending to premature exhaustion.

It was to test the validity of this premise, as applied to polycythemia vera, that this study was undertaken. The administration of phenylhydrazin hydrochloride by mouth, or radiation over spleen and long bones, has gradually replaced venesection as a method of reducing the red cells and hemoglobin in polycythemia vera. For this reason, the effects of these three methods of treatment on the bone marrow have been studied to yield a basis for comparisons. In addition, these same observations were extended to other types of polycythemia, giving a further basis for comparison.

The bone marrow reactions to phenylhydrazin in the treatment of polycythemia, have been studied and recorded by several observers and data are available in the literature.[1, 2, 3, 4, 5] No references were found recording the effects of venesection on the bone marrow in polycythemic states, nor were any observations found on the reticulocyte response to roentgen-ray treatment of polycythemia.

Terminology

Polycythemia vera is used to designate the syndrome known as Vaquez-Osler disease, or erythremia. This syndrome is an absolute polycythemia with a palpable spleen and no definite lesions of the heart or lungs. There is no demonstrable cause for the high hemoglobin and red cell level. Polycythemia or erythrocytosis refers to an increased red cell and hemoglobin level secondary to pulmonary or cardiac disease, or some other definite lesion accounting for the abnormal red cell formation.

Polycythemia hypertonica refers to the syndrome described by Geisböck.[6] It occurs in individuals with hypertension and arteriosclerosis, who show an erythrocytosis with or without an enlarged spleen. The condition may disappear or it may be quite similar in its course to polycythemia vera. It is probable that some of these cases are really polycythemia vera. Where the

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term radiation is used it refers to roentgen-ray as no radium or other type of radiant energy was used.

Method and Technic

The method of procedure in these studies was to use as an index of bone marrow function the reticulocyte count. This method is our nearest approach to a direct measure of marrow activity. It is well known in connection with the work of Minot and Murphy,[7] in treating pernicious anemia by whole liver and liver fractions. The normal reticulocyte per cent is usually given as between 0.4 and 1.5.

The fluctuations in the percentage of reticulocytes in the peripheral blood have been tabulated with the hemoglobin and formed elements of the blood, as the different methods of treatment were carried out. It should be stressed that the main objective of these studies is to observe and record the reticulocyte per cent, as an index of bone marrow reaction to the different forms of treatment employed.

The blood counts were made, more than one hour after meals, with pipettes certified by the U. S. Bureau of Standards. Neubauer counting-chambers were used. Hemoglobin estimations were made on the Sahli instrument calibrated so that 13.7 gm. equal 100 per cent hemoglobin. Blood smears were stained by the Jenner-Giemsa method and reticulated counts were made on cover slips prepared with a film of cresyl blue counterstained by Jenner-Giemsa stains, according to the method of Cunningham.[8] All of the reticulated cell counts were checked by the author and the percentage was estimated by counting the number of reticulated cells per one thousand erythrocytes.

The majority of the venesections were performed by inserting a large caliber needle in the median basilic vein and allowing the blood to flow into an open vessel. The most satisfactory method was the use of a Vincent transfusion tube attached to the needle, negative pressure being induced by a rubber bulb fixed to the top of the tube. If everything is in readiness the actual bleeding requires about 15 minutes.

The roentgen-ray exposures were as follows: *

Case Number 1

Dates	*Treatments*
Nov. 17, 1932 to Nov. 21, 1932	Four exposures to spleen, anterior and posterior, alternating. Patient received 400 r. measured in air (assumed to be 50 per cent S.E.D.).†
Dec. 7, 1932 to Jan. 5, 1933	Twelve treatments over long bones, tibiae, fibulae, radii, ulnae, humeri, femora. Dose 160 to 200 r. measured in air. *Set-up 200 K.V. constant potential. Skin target distance 60 cm. filtered through .5 mm. copper plus 1 mm. aluminum.*

* Roentgent-ray treatments were given under the direction of Dr. Robert S. Stone, in charge of the Department of Roentgenology, University of California Hospital.

† Skin Erythema Dose.

CASE NUMBER 2

Dates	*Treatments*
Oct. 6, 1932 to Oct. 21, 1932	Seven exposures to spleen anterior and posterior, alternating. Patient received 200 r. measured in air (assumed to be 25 per cent S.E.D.).†
Oct. 25, 1932 to Nov. 15, 1932	Four treatments over chest anterior and posterior, alternating—dose 200 r.
Dec. 6, 1932 to Dec. 13, 1932	Four treatments over long bones, tibiae, fibulae, radii, ulnae, humeri, femora. Dose 108 r. measured in air (assumed to be 15 per cent S.E.D.).†
	Set-up 200 K.V. constant potential. Skin target distance 50 cm. filter .5 mm. copper plus 1 mm. aluminum.

CASE NUMBER 3

Dates	*Treatments*
Sept. 26, 1932 to Sept. 27, 1932	Two exposures to spleen anterior and posterior. Patient received 400 r. measured in air (assumed to be 50 per cent S.E.D.).
Nov. 4, 1932 to Nov. 9, 1932	Four treatments over spleen anterior and posterior, alternating. Patient received 400 r. measured in air (assumed to be 50 per cent S.E.D.).
Dec. 5, 1932 to Dec. 8, 1932	Four treatments over long bones, tibiae, fibulae, radii, ulnae, humeri, femora. Patient received 160 r. (20 per cent S.E.D.).
	Set-up 200 K.V. constant potential. Skin target distance 60 cm. filter .5 mm. copper plus 1 mm. aluminum.

MATERIAL

In order to secure an idea of the normal daily variation in the reticulocyte count, a graph of daily estimations was secured from counts on the author, a normal individual from the hematological standpoint.

Normal Daily Variation of the Reticulocyte Count in Author

	Hgb.	R.B.C.	W.B.C.	Retics.	P.M.N.		E.	B.	Lymph.	Monos.	Platelets
12.27.32	90	4,740,000	7,050	0.2	53	16* / 37†	2	2	36	7	290,000
12.28.32	87	4,910,000	4,350	0.0	54	18 / 36	3		38	5	330,000
12.29.32	84	4,870,000	5,100	0.5	59	16 / 43	4		29	8	240,000
12.30.32	85	4,750,000	6,900	0.6	61	20 / 41	2		29	8	270,000
12.31.32	92	4,890,000	5,400	0.2	60	22 / 38	5	1	22	12	330,000
1.1.33	95	4,650,000	9,800	0.9	55	9 / 46	9		25	11	
1.2.33	95	4,490,000	7,600	1.3	56	22 / 34	1	1	36	6	
1.3.33	95	4,910,000	7,250	0.9	54	14 / 40	2		35	9	
1.4.33	102	5,320,000	10,200	0.9	62	20 / 42	3		29	6	370,000
1.5.33	95	5,130,000	10,350	1.5	62	16 / 46	2		22	14	370,000
1.6.33	98	5,460,000	10,550	1.0	68	20 / 48	5		18	9	290,000
1.7.33	95	4,790,000	9,350	1.2	57	20 / 37		1	30	12	340,000
1.11.33	91	4,840,000	7,200	1.0	57	17 / 40	2	1	34	6	220,000
1.14.33	89	4,880,000	7,500	1.8	54	19 / 35	9		30	7	
1.17.33	85	5,010,000	9,100	1.0	52	10 / 42	1	1	32	14	270,000

Note: In the P.M.N. the number of neutrophiles are divided into non-filament above (*) and filament below (†).

Four patients with polycythemia were studied:

CASE I

A female patient, aet. 54, married, no children, who first came under observation at aet. 38 years. Her clinical and laboratory findings were reported in detail by Hurwitz and Falconer [9] in 1918.

The diagnosis of polycythemia vera was made on the following findings: marked acro-cyanosis, palpable liver, and enlarged palpable spleen; absence of pulmonary and cardiac symptoms and abnormal physical findings; a long remission of over ten years, following benzol by mouth and roentgen-ray over the spleen.

Laboratory data October 11, 1916: hemoglobin 128 (Fleischl); red blood cells 10,064,000; white blood cells 9800; neutrophiles 69; eosinophiles 0; lymphocytes 21; monocytes 8; myelocytes 2. Viscosity (Hess Viscosometer) 7.7 (normal 4.5). Prothrombin determination normal. Electrocardiogram: heart within normal limits. Blood non-protein-nitrogen 43.9 mg.; urea nitrogen 14 mg. Urine: amber, acid, specific gravity 1.020; albumin 0; sugar 0; casts 0; cells—few epithelial.

This patient, according to her history, is now in the nineteenth year of her disease. She has responded well to the following treatments:

Venesection (1915), benzol and radiation (1916) [8]; phenylhydrazin (1929–1930); roentgen-ray over the spleen (1928); venesection (1931); roentgen-ray over spleen and long bones (1932); phenylhydrazin (1932).

The disease for the past eighteen months has been pursuing the course of a mild polycythemia with few symptoms. As we have data extending over several years, a good base line has been established. For these reasons she was selected as a suitable patient to compare the effects of venesection, phenylhydrazin and radiation on the bone marrow, as evidenced by the reticulocyte response.

She was treated first by venesection until the red cell count fell to 4.64 million, hemoglobin 75 per cent. Treatment was now stopped and the red cell count was allowed to return to the pre-venesection level. Next she was given acetyl phenylhydrazin 0.1 gm. daily for 14 days, the red cells again being allowed gradually to return to pre-treatment level. The same procedure was followed out with radiation by roentgen-ray.

CASE II

A Polish Jew, aet. 45, divorced. First seen August 25, 1932, complaining of dyspnea, abdominal pains and headache. He gave a history of having polycythemia for the past nine years. For about five years he was under the care of a physician in New York City. According to his statement, he took 100 mg. phenylhydrazin daily for 10 days of each month, for about two years. Also he had two courses, of 48 treatments each, of radiation over the long bones. He has epistaxis two or three times yearly which affords considerable relief. Bleeding has always given prompt relief. He has taken treatments wherever he happened to be, as he has moved about considerably.

Examination showed face, neck and extremities cyanotic. Moderate degree of pulmonary emphysema; cardiac hypertrophy and dilatation. Blood pressure 130 systolic and 80 diastolic. Liver enlarged and tender; spleen enlarged 6 cm. below the costal border in the mid-clavicular line, not tender.

Laboratory: Hemoglobin 115; red blood cells 10,450,000; white blood cells 28,000; red blood cells show poikilocytosis and anisocytosis. Many large oval forms. Many rod-shaped cells. Urine showed heavy trace of albumin; 6–8 pus cells; 1–3 red blood cells per high dry field; 4–5 hyaline and granular casts per low power field. Basal metabolic rate 7 per cent plus. Oxygen capacity of blood 16.46 volume per cent. Blood sugar 102 mg. per 100 c.c.

There is a possibility of the erythrocytosis, in this patient, being connected with a pituitary tumor (presumably a basophilic adenoma). The following findings suggest this diagnosis.

Roentgenogram findings suggestive of a pituitary tumor, a question of temporal narrowing of the fields of vision, exophthalmos, adiposity of face, neck and trunk, loss of libido, loss of hair, dusky congested skin, pigmentation of skin, polyphagia, polydipsia, polyuria.

Case III

Female, aet. 68. Admitted to University of California Hospital, March 19, 1928. Past History: Malaria aet. 20. Aet. 43 took five drops of Fowler's solution for one year for "eczema." Menopause aet. 45, uneventful. Appendectomy and cholecystectomy aet. 67 (1927), good recovery; much dental work, bleeding gums past four or five years.

Complaints: Weakness and swelling of lower extremities since 1923 (five years), burning of hands and feet, dizziness, failing vision, memory "bad." Thickness of tongue and difficult speech for two weeks before being seen March 19, 1928. Examination: cyanosis of face, hands and feet; peripheral arteries sclerotic; radial arteries beaded; blood pressure 210 systolic and 100 diastolic; heart slightly enlarged to the left; heart sounds good quality, no murmurs heard; second aortic sound greater than second pulmonic; chest shows moderate pulmonary emphysema; abdomen: liver enlarged, about six centimeters below the costal border in the right mid-clavicular line; spleen palpable, edge sharp and tender.

Laboratory: Blood: hemoglobin 85; red blood cells 8,200,000; white blood cells 10,150; neutrophiles 64; lymphocytes 35; monocytes 1; urine, specific gravity 1.015; acid; albumin moderate trace; sugar 0; sediment, few pus cells, occasional granular and hyaline cast. Phenolsulphonephthalein 30 per cent first hour, 12 per cent second hour, total 42 per cent. Ewald test meal, no free HCl, low total acid, no blood. Electrocardiogram rate 88, regular rhythm; somatic tremor in Lead I; within normal limits. Wassermann negative; blood chemistry, urea nitrogen 15.6 mg.; non-protein-nitrogen 46.1 mg. Stool negative for parasites, ova and blood.

Patient had two courses of phenylhydrazin hydrochloride. The first totaled four grams in 16 days. Red cells dropped to 3,030,000 with 50 per cent hemoglobin; white blood cells 20,900 with 82 per cent neutrophiles. She began to complain of numbness and loss of motor power in the left arm and hand and a left facial weakness was noted. Phenylhydrazin was discontinued. The second course was given in another city after she left the hospital. This course was accompanied by loss of memory, so the drug was discontinued.

Diagnosis: Polycythemia hypertonica (Geisböck's syndrome).

Results

It will be noted that each table has a graphic chart accompanying it, bearing the same number. The graphic chart shows the general results of the experiment, the table giving the details.

Case No. 1, Chart No. 1 and Table No. 1 show the results of 10 venesections given to this patient. These procedures were distributed over a continuous period from June 18, 1931 to November 4, 1931. There was an average, roughly, of two venesections per month for five months (169 days). The first three venesections were performed every fourth day, three full days elapsing between. The highest reticulocyte rise of this first experimental period was 2.2 per cent, occurring four days after the third venesections.

TABLE I

CASE 1

1931		Hgb. per cent	R.B.C. millions per cu. mm.	Retic. per cent	W.B.C. thousands per cu. mm.	P.M.N. per cent	P.M.E. per cent	P.M.B. per cent	Lymph. per cent	Monoc. per cent
June	11	129	9.84	0.2	11.2	78			17	4
	18				Venesection—300 c.c.					
	19		9.22	0.3	6.0	57			38	5
	20		8.65	0.6	4.2	75	1		17	7
	22		8.43	0.9	6.1	69		1	27	3
	23				Venesection—200 c.c.					
	24		9.08	1.0	11.6	75			21	4
	25		9.17	0.9	7.4	67	3		26	4
	26		8.22	1.2	6.7	60	1		35	4
	26				Venesection—600 c.c.					
	27		7.99	1.8	8.6	65	1		25	9
	29	114	8.27	1.5	9.0	74	1		21	4
	30		7.28	2.2	9.4	74		1	22	3
July	1		7.69	0.8	8.9	60			37	3
	2		7.80	0.6	10.9	61	1		36	2
	3		7.60	0.2	9.4	70			26	4
	6	116	7.54	0.6	8.6	78	1		17	4
	7		7.24	1.6	10.0	74			21	5
	8		6.94	1.5	11.1	64		1	33	2
	8				Venesection—600 c.c.					
	9		7.54	1.6	12.2	74			24	2
	10		7.35	0.1	13.2	72		1	25	2
	11		7.31	0.8	15.5	64	1		31	4
	13	106	6.74	0.5	10.5	72	1		22	5
	14		6.90	0.8	13.4	50	2		43	5
	15		6.40	0.8	12.8					
	16		6.24	0.7	11.6	61			34	5
	17		8.05	0.7	11.0	61	1		32	6
	18	106	7.54	1.0	12.8	73			23	4
	20		6.84	0.3	11.0	66			30	4
	21		7.12	0.2	10.2	76	1		17	6
	22		7.45	0.4	9.9	69			26	5
	23		7.32	1.1	9.9	67			28	5
	23				Venesection—500 c.c.					
	24		6.71	0.6	11.2	57			36	7
	25		7.00	0.7	10.4	69		1	26	4
	27		6.92	0.8	9.9	74			21	5
	28		6.75	0.1	12.6	72		1	25	2
	29		6.91	0.8	9.0	67			27	6
	30		6.89	1.2	9.4	71	1		24	4
	31		6.44	0.8	9.0	63			34	3
Aug.	1		6.67	0.8	11.1	65	1		27	7
	3		6.48	0.6	8.6	73	2		22	3
	4		6.20	0.8	8.7	67	2		26	5
	5		6.24	1.0	6.1	71	1	1	20	7
	6		6.80	0.9	6.8	71	1		24	4
	6				Venesection—600 c.c.					
	7		6.55	1.1	8.5	72			19	9
	8		6.08	0.9	10.8	70			22	8
	10		5.79	1.2	7.8	75			22	3
	11		5.91	1.4	10.4	73	1	1	15	10
	12		5.72	1.2	7.1	68			25	7
	13		5.67	0.5	8.0	64			31	5
	14		5.86	0.8	5.1	76			20	4
	15		6.12	0.8	7.0	74	1		23	2
	17		6.15	0.7	7.0	64			32	4
	18		6.18	0.7	6.4	70	2	1	21	6
	19		6.30	1.0	10.1	65	1	2	23	9
	20		6.28	0.3	7.3	64	1		23	12
	21		6.59	0.2		70		1	24	5

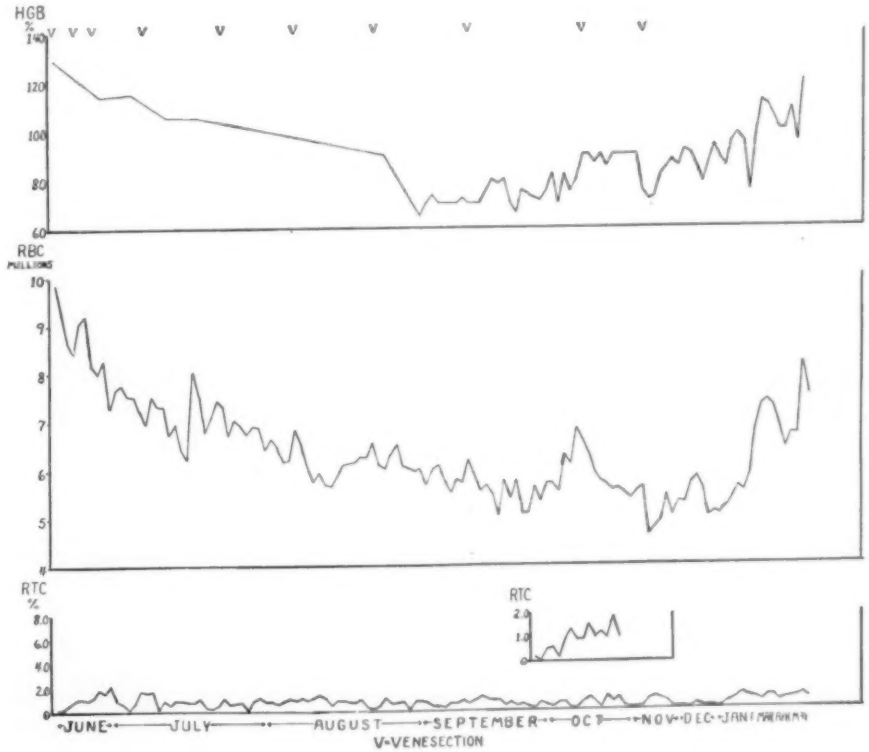
TABLE I (*Continued*)

1931		Hgb. per cent	R.B.C. millions per cu. mm.	Retic. per cent	W.B.C. thousands per cu. mm.	P.M.N. per cent	P.M.E. per cent	P.M.B. per cent	Lymph. per cent	Monoc. per cent
	21				Venesection—300 c.c.					
	22		6.12	0.4	9.6	59			28	13
	24	90	6.03	1.1	7.3	55			34	11
	25		6.33	0.6	7.8	67			29	4
	26		6.54	0.7	7.4	64			29	7
	27		6.17	0.8	11.7	73			21	6
	28		6.08	0.1	9.0	77	1		16	6
	29		5.97	0.8	8.8	75		1	16	8
	31	65	6.01	0.8	7.3	71			24	5
Sept.	1	70	5.75	0.7	6.0	70			24	6
	2	73	6.01	0.4	5.8	52		1	38	9
	3	70	6.11	0.4	5.4	65			28	7
	5		5.77	0.3	6.6	53	2		37	8
	8	70	5.55	0.6	9.1	69			30	1
	10	70	5.84	0.6	7.5	70			25	5
	11	72	5.72	0.8	4.3	66	1		25	8
	12	70	6.20	0.6	6.0	66	1		28	5
	12				Venesection—400 c.c.					
	14			0.8		62	1		26	11
	15	70	5.58	1.2	5.8	58		1	35	6
	16	75	5.68	0.9	5.4	59			32	9
	17	80	5.48	0.8		67	1		27	5
	18	78	5.09	0.8	6.3	57			37	6
	19	80	5.79	0.4	9.2	62			31	7
	21	70	5.40	0.6	7.9	66			26	8
	22	66	5.78	0.4	4.8	60			32	8
	23	75	5.13	0.5	9.6	73	1		22	4
	25	73	5.17	0.3	7.6	69	1		24	6
	26		5.69	0.2		70			20	10
	28	72	5.30	0.6	5.3	73			22	5
	30	75	5.72	0.4	5.4	59			32	9
Oct.	2	82	5.74	0.3	6.9	55			38	7
	5	70	5.56	0.6	10.3	70		1	25	4
	7	82	6.30	0.6	6.9	59		1	32	8
	9	75	6.11	0.2	6.5	62			30	8
	12	80	6.89	0.2	8.2	57	1		34	8
	14	90	6.67	0.6	10.4	54		1	32	12
	14				Venesection—600 c.c.					
	15	90	6.39	1.0	10.4	71			18	11
	17	87	5.93	0.6	8.9	52			38	10
	19	90	5.78	0.2	9.2	65			34	1
	21	85	5.72	1.2	9.1	67			23	9
	23	90	5.65	0.6	8.3	66		1	26	8
	26	90	5.67	0.1	11.3	62	1	1	31	3
	28		5.50	0.3	9.4	68	1	2	23	6
	30		5.39	0.2	8.6	73	1		22	4
Nov.	2	90	5.53		8.8	63			29	8
	4	90	5.61	0.3	8.7	61	1		32	6
	4				Venesection—350 c.c.					
	6	75	4.64	0.8	8.4	53		3	36	8
	9	72	4.80	1.0	9.6	68		3	20	9
	14	73	4.90	0.8	8.3	58		2	30	10
	17	82	5.48	0.6	9.9	70	1		20	9
	20		5.04	0.2	8.0	59	1	1	33	6
	23	87	5.34	0.2	9.7	65		1	28	6
	27	85	5.30	0.2	8.2	68		2	26	4
Dec.	1	92	5.73	0.1	10.4	54	1	1	33	11
	4	90	5.88	0.4	8.4	72		2	20	6
	9	85	5.66	0.2	8.1	49	1	1	36	13
	17	78	5.03	0.2	8.4	61	1		30	8
	23	85	5.17	0.1	8.6	73	2		16	9
	28	93	5.11	0.1	8.1	66	2		26	6

TABLE I (*Continued*)

1932		Hgb. per cent	R.B.C. millions per cu. mm.	Retic. per cent	W.B.C. thousands per cu. mm.	P.M.N. per cent	P.M.E. per cent	P.M.B. per cent	Lymph. per cent	Monoc. per cent
Jan.	5	88	5.23		10.6					
	8	85	5.43	0.7		74			18	8
	13	95	5.65	1.0	11.0	67	1	2	26	4
	16	98	5.56	1.2	8.0					
	21	85	5.88	0.8	9.7					
	27	75	6.62	0.8	6.9	68	1		24	7
Feb.	13	97	6.81	0.6	7.8	72	1		26	1
Mar.	5	112	7.34	1.0	8.5	58			30	12
	8	110	7.40	1.0	10.2	57	2		29	12
	11	105	7.31	0.6	10.6	68	1		26	5
	15	100	6.89	0.7	12.1	62	1	1	28	8
Apr.	1	100	6.44							
	13	108	6.71	0.9	13.4	61			27	12
	20	95	6.70	1.2	10.3	64			29	7
May	16	120	8.16	0.8	9.4	72		2	20	6
	18		7.54	0.6	8.7	76	1	3	14	6

CASE 1—CHART 1



After each bleeding, the reticulocyte count rose to between 1 and 2 per cent, the rise occurring between 24 hours and four days (96 hours). It will be noted in inspecting Table No. 1 and Chart No. 1, that the reticulocyte count during the venesection treatment period varied within narrow limits. The average count for the period was .4 per cent.

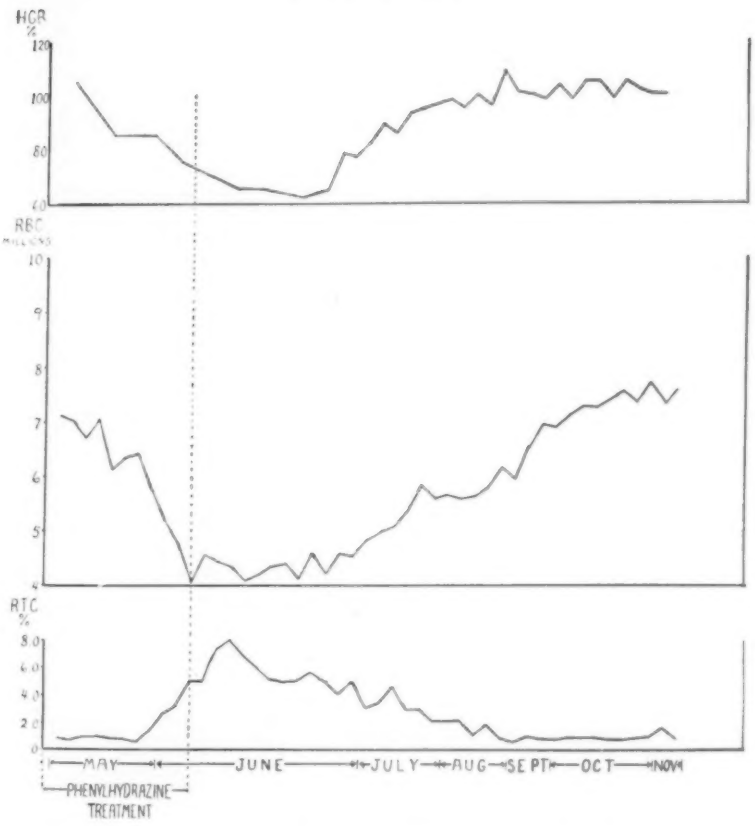
TABLE II

CASE 1

1932		Hgb. per cent	R.B.C. millions per cu. mm.	Retic. per cent	W.B.C. thousands per cu. mm.	P.M.N. per cent	P.M.E. per cent	P.M.B. per cent	Lymph. per cent	Monoc. per cent
					Started Phenylhydrazin					
May	18								41	12
	19		7.13	0.8	12.7	47			25	6
	20	105	7.06	0.7	13.6	69			36	7
	21		6.81	0.9	8.5	57		4	31	4
	23		7.09	1.0	8.0	61			29	4
	24	85	6.14	0.8	9.2	67			24	9
	25		6.31	0.8	12.1	67			29	8
	26		6.40	0.6	11.6	63			26	13
	31	85	5.84	1.3	13.4	61			19	5
June	1		5.18	2.6	12.8	74	1	1	30	11
	3	75	4.84	3.3	11.2	59				
	5				Stopped Phenylhydrazin					
	6	63	4.02	5.0	11.5	67			27	6
	7		4.54	5.0	10.9	77			16	7
	8		4.43	7.4	10.2	70			28	2
	9	66	4.31	8.0	11.2	69	2	2	23	4
	10		4.07	6.8	9.6	68	2	2	21	7
	13	65	4.19	6.0	8.4	63	5	1	25	6
	15		4.31	5.2	9.6	71			26	3
	17		4.35	5.0	7.9	69	1		22	8
	20	62	4.10	5.1	9.6	71			21	8
	22		4.61	5.6						
	25	65	4.20	5.0						
	27	78	4.58	4.2	12.1	71		1	26	2
	29	77	4.55	5.0						
July	1	82	4.81	3.2	7.2	62	1	1	31	5
	6	89	4.97	3.5						
	9	86	5.08	4.3	7.1	73		1	22	4
	12	93	5.39	3.0	7.8	65			29	6
	15	95	5.84	3.0						
	19	97	5.60	2.1	7.7	71			21	8
Aug.	2	98	5.68	2.1	6.1	67			24	9
	9	95	5.63	2.1						
	11	100	5.65	1.2	7.1	63	1		29	7
	15	96	5.78	1.8						
	26	109	6.15	0.9	6.9	65	1		30	4
Sept.	2	101	5.93	0.6	8.3	58	2	1	31	8
	8	100	6.52	1.0	8.4	62			29	9
	17	98	6.95	0.8	5.7					
Oct.	4	103	6.90	0.8	8.6					
	7	98	7.13	1.0	6.7	56	1		34	9
	10	105	7.27		5.6					
	13	105	7.26	0.9	7.0	65		1	27	7
	17	98	6.86	0.8	5.8	69		1	26	4
	21	105	7.57	0.8	7.8	68	2	3	22	5
	28	102	7.38	0.9	8.9	78			18	4
	31	100	7.71	1.0	10.2	70			18	12
Nov.	5	100	7.32	1.6	10.2	70			26	4
	10		7.66	0.9	7.3					

Chart No. 2 and Table No. 2. The last venesection was November 4, 1931. No further treatment was given, the red cells and hemoglobin were allowed to rise until, by May 16, 1932, the hemoglobin had gone up to 120 per cent and the red cells to 8.16 million. On May 18, 1932 patient was started on acetyl phenylhydrazin (pyrodin) 0.1 gram daily for four days or

CASE 1—CHART 2



a total of 1.4 grams. There was a prompt fall in hemoglobin and red cells as is characteristic of this hemolytic agent. The reticulocytes began to rise about the sixth day after the drug was started and increased rapidly to 8 per cent, falling very slowly and gradually. Even as long as 65 days after phenylhydrazin was stopped, the reticulocyte per cent was 1.2 which corresponds to the highest reticulocyte per cent during the venesection treatment period.

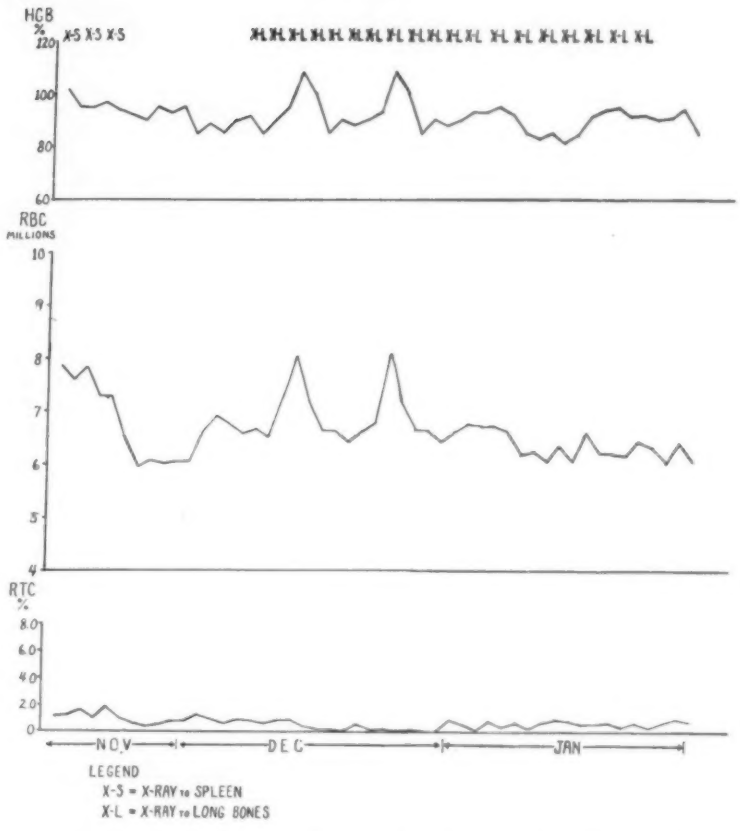
Chart No. 3 and Table No. 3. The red cells and hemoglobin following administration of phenylhydrazin were allowed to return to the level at which phenylhydrazin was begun, which occurred by November 17, 1932. On this date radiation was begun. Three exposures over the spleen with deep roentgen therapy were carried out at three day intervals. After two weeks, as there was only approximately one million reduction in her red cells, radiation was again given over the long bones, twelve treatments being administered. The reticulocytes were 1.2 per cent at the beginning of the treatment and none was noted on January 5, 1933, the date of the last treatment. The highest rise was 1.8 per cent, six days after radiation was begun, and it will be noted that the daily variation was within a very narrow range.

TABLE III

CASE 1

1932		Hgb. per cent	R.B.C. millions per cu. mm.	Retic. per cent	W.B.C. thousands per cu. mm.	P.M.N. per cent	P.M.E. per cent	P.M.B. per cent	Lymph. per cent	Monoc. per cent
Nov.	17	102	7.84	1.2	8.2	68			28	4
	17				X-ray to Spleen					
	18	95	7.63	1.3	5.2	68	1		19	12
	18				X-ray to Spleen					
	19	95	7.80	1.6	8.7	72			14	14
	21	97	7.30	1.0	6.4	76	1		15	8
	21				X-ray to Spleen					
	22	94	7.29	1.8	10.0	85	1	1	9	4
	23		6.49	1.0	8.4	80	2		9	9
	25	90	5.96	0.6	6.3	83			8	9
	26	95	6.20	0.4	7.3	85	1		5	9
	28	93	6.04	0.5	3.7	74	2	2	12	9
	30	95	6.10	0.8	5.5	86		1	10	13
Dec.	1	85	6.08	0.8	7.8	68		2	16	12
	2	88	6.68	1.3	6.8	79	1		14	6
	3	85	6.90	0.9	9.5	81			11	8
	5	90	6.78	0.6	7.1	76		1	20	2
	6	92	6.66	0.9	6.6	75	1	1	16	6
	7	85	6.74	0.8	8.1	69	2	2	22	5
	7				X-ray to Long Bones					
	8	90	6.55	0.7	10.0	77		1	13	9
	9	95	7.26	0.9		68	1		18	12
	9				X-ray to Long Bones					
	10	108	8.05	0.9	13.0	74		3	18	5
	12	100	7.20	0.4	11.2	72	1		18	8
	12				X-ray to Long Bones					
	14	85	6.68	0.2	7.8	64	2		23	11
	14				X-ray to Long Bones					
	16	90	6.67	0.2	9.8	70	1	1	22	6
	16				X-ray to Long Bones					
	19	88	6.44	0.5	5.5	76		1	17	6
	19				X-ray to Long Bones					
	21	90	6.67	0.0	7.1	80	1	2	15	2
	21				X-ray to Long Bones					
	22	93	6.80	0.2	9.3	86	1	1	8	4
	23	93	6.77	0.1	7.5	72			21	7
	23				X-ray to Long Bones					
	27	95	6.77	0.1	6.5	69			19	12
	27				X-ray to Long Bones					
	28	92	6.65	0.1	6.2	75	2		13	10
	29	85	6.19		5.5	66	3	1	19	11
	29				X-ray to Long Bones					
	30	83	6.24	0.0	4.1	61			25	14
	31	85	6.07	0.0	4.4	78		1	15	6
	31				X-ray to Long Bones					
Jan.	3	82	6.32	0.9	5.3	77	1		16	6
	3				X-ray to Long Bones					
	4	84	6.05	0.5	6.2	76	1		15	8
	5	92	6.63	0.0	5.2	70			21	9
	5				X-ray to Long Bones					
	6	94	6.24	0.8	6.6	71	1		17	11
	7	95	6.23	0.4	7.4	58			23	13
	9	92	6.20	0.7	4.1	75	1		16	7
	10	92	6.45	0.3	7.6	81			13	6
	12	90	6.31	0.7	4.6					
	13	91	6.02	1.0	6.4	72		1	15	12
	16	94	6.40	0.8	5.8	59			32	9

CASE 1—CHART 3



Case No. 2, Chart No. 4 and Table No. 4 show the effects of venesection and of radiation in polycythemia secondary to chronic asthma and pulmonary emphysema. The venesections were not uniform in amount, two of them being under 400 c.c. due to technical difficulties in bleeding the patient. It will be noted, however, that on December 29, 1932, after the radiation had reduced his cells to below five million, he was bled 850 c.c. On the fifth day following, the reticulocyte per cent was 2.2, the highest rise of the experiment, including both venesection and radiation. The reticulocyte fluctuation during both venesections and radiation was within narrow limits. Exclusive of the last venesection, which came after the course of radiation, the reticulocyte per cent varied between 0.1 and 1.4 in both types of treatment.

Case No. 3, Table No. 5. This patient showed an acute polycythemia and was quite ill. As soon as his symptoms were relieved by venesection, he would leave the hospital, going to his home in another city, returning again when symptoms became distressing. He was not a coöperative patient for purposes of treatment, however his table shows very well the effects of large venesections combined with radiation over the long bones in an acutely ill polycythemia, possibly of the secondary type (see case record).

TABLE IV

CASE 2

1931	Hgb. per cent	R.B.C. millions per cu. mm.	Retic. per cent	W.B.C. thousands per cu. mm.	P.M.N. per cent	P.M.E. per cent	P.M.B. per cent	Lymph. per cent	Monoc. per cent
Nov. 3	110	6.90							
11	108	6.10							
1932									
Jan. 21	117	6.40	0.3	6.3	62	2		24	12
25	112	6.23	0.2	4.4	51			34	15
26	108	5.95	0.2	6.9	62	1		33	4
26				Venesection—375 c.c.					
27	100	4.92	0.1	5.8					
Feb. 1	90	4.32	0.1	5.6					
3	90	4.17	0.3	4.6	60			29	11
9	100	4.80	0.1	4.3	73	2		18	8
12	95	4.50	0.6	10.8	69			22	9
15	96	5.00	0.3						
19	107	5.18	0.2	5.4					
20				Venesection—500 c.c.					
23	104	4.92	0.2	6.1					
25	83	4.36	0.7						
29	95	5.21	0.6						
Mar. 2	100	5.21	1.4	4.8	57	1	1	29	12
4	103	5.14	1.1						
7	96	5.02	1.2						
10	90		0.9	4.7					
15	100	5.42	1.1		69	2		24	5
17	100	5.02	0.8						
28	99	4.91	0.8						
30	100	5.47	1.0	3.7	52	2		34	12
Apr. 4	110	5.44	0.4	5.4					
8		5.63							
19	110	5.83	0.6		54			36	10
26	104	4.90	0.2						
May 2	92	4.90	0.4	6.2					
9		5.22							
16	100	4.92	0.2						
June 3	102	5.18	0.4						
6		5.98	0.1						
7				Venesection—600 c.c.					
8	88	5.19	0.2						
13	102	5.48	0.2						
21	103	4.61	0.9						
24	102	5.28		5.2	56	4		32	8
Sept. 20	105	5.73	0.2	4.1					
20				Venesection—350 c.c.					
21	103	4.75	0.2	6.1	45	2		41	12
23	100	5.05	0.4	5.6	56	2		32	10
24	110	5.04	0.4	3.9	55	1		32	12
27	102	5.40	1.0	4.3	62	2		25	11
Oct. 3	105	5.34	0.6	6.8	56	2		35	6
6	103	5.18	0.8	5.0	45	2		42	11
6				X-ray to Spleen					
8	110	5.12	0.9	4.9	57	1		32	10
8				X-ray to Spleen					
11	105	5.37	0.6	4.7	55	2		28	15
11				X-ray to Spleen					
13	100	5.25	0.2	4.4	69	1		18	12
13				X-ray to Spleen					
15	104	5.24	0.6	4.5	72	1		17	10
15				X-ray to Spleen					
18	95	4.95	0.4	4.0	66	1		24	9
18				X-ray to Spleen					
21	93	5.20	0.2	4.5	66	1		25	8

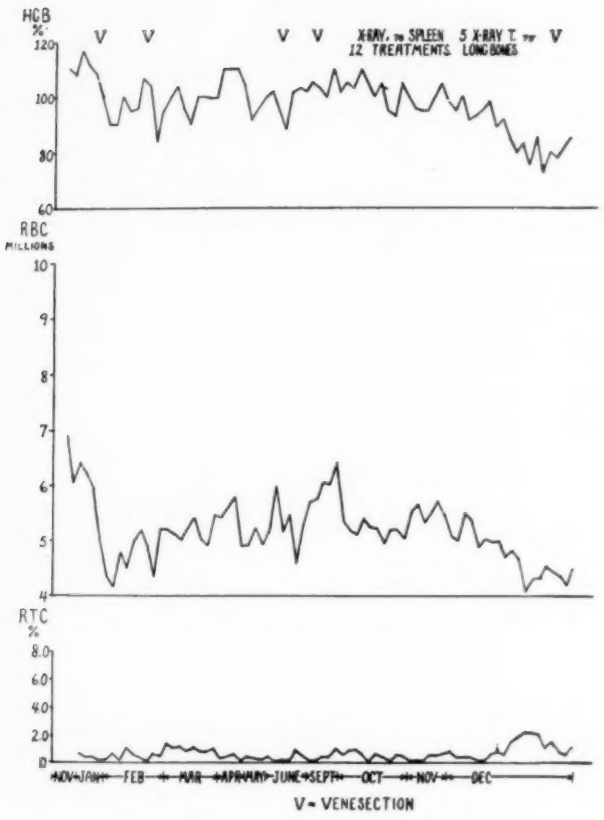
TABLE IV (*Continued*)

1932		Hgb. per cent	R.B.C. millions per cu. mm.	Retic. per cent	W.B.C. thousands per cu. mm.	P.M.N. per cent	P.M.E. per cent	P.M.B. per cent	Lymph. per cent	Monoc. per cent
Oct.	21				X-ray to Spleen					
	25	105	5.21	0.5	3.9	68	1		16	15
	25				X-ray to Spleen					
	28	101	5.06	0.4	4.9	68	2	1	15	14
	28				X-ray to Spleen					
Nov.	10	96	5.52	0.2	3.6	70	2		14	4
	10				X-ray to Spleen					
	12	95	5.62	0.2	4.9	60	3		18	19
	15	95	5.31	0.2	5.4	64	2		26	8
	15				X-ray to Spleen					
	19	100	5.50	0.5	4.2	52	5		27	16
	19				X-ray to Spleen					
	25	104	5.67	0.5	4.0	70	1	1	13	13
	30	98	5.49		4.4	70	1		15	14
Dec.	5	95	5.14	0.8	4.2	66	2		16	16
	5				X-ray to Long Bones					
	6				X-ray to Long Bones					
	7				X-ray to Long Bones					
	8				X-ray to Long Bones					
	8	100	5.01	0.4	4.0	60	3		19	17
	13	92	5.50	0.4	5.9	77	1		12	10
	15	93	5.34	0.4	6.4	72	2		12	14
	15				X-ray to Long Bones					
	19	95	4.88	0.2	5.9					
	20	98	5.03	0.2	5.9	74	1		15	10
	21	89	4.99	0.7		66	1		20	12
	24	92	5.00	0.8	4.9					
	27	85	4.74	0.6	8.2	67	4		19	10
	29				Venesection—850 c.c.					
	30	80	4.87	1.5	7.4	80	2		7	11
	31	83	4.71	1.9	5.4	71	2	1	15	11
1933										
Jan.	3	76	4.10	2.2	5.9	78			15	7
	6	85	4.29	2.2	7.4	77	1	1	14	7
	8	73	4.32	2.0	5.8	71	4		16	9
	10	80	4.54	1.1	6.7	75	2		17	6
	11	78	4.44	1.5	5.6	65	2		27	6
	13	82	4.35	0.8	4.7	66	3		18	13
	14	85	4.21	0.6	6.0	61	4		20	15
	16		4.52	1.2	7.9	76			14	10

Here again the reticulocyte response was within a very narrow range. The per cent level is slightly higher throughout than in the other experiments where the same agents are employed. This reticulocyte level certainly suggests a slightly over-active marrow, yet venesection of as much as 900 c.c. did not appreciably increase the marrow activity.

Case No. 4, Table No. 6. This patient, an elderly woman with hypertension (polycythemia hypertonica), had three venesections during a 27 day period of experimental observation. The reticulocytes did not rise above 1.8 per cent and the fluctuation was within a very narrow range. The amount of blood withdrawn at each bleeding was comparatively small on account of the danger in this type of case, that withdrawing too much blood may produce thrombosis, either of veins or small arteries, especially a cerebral artery. Relief of symptoms should be the objective.

CASE 2—CHART 4



DISCUSSION

Case No. 1 was an especially favorable patient for a study of this type. She has been under observation for seventeen years and the response of her disease to various forms of treatment is well known. For the past four years her symptoms have been mild, responding well to phenylhydrazin and to venesection. The response to radiation has not been so satisfactory. I have purposely tried to guard against untoward results during these experiments, as such results would probably result in loss of coöperation and opportunity for future studies. The withdrawal of an amount of blood exceeding 600 c.c. was considered to involve a risk of thrombosis.

Analysis of the effects of venesection as compared to acetyl phenylhydrazin, on the bone marrow shows a striking difference in the reticulocyte response; acetyl phenylhydrazin producing a rise as high as 8 per cent, while venesection showed no definite change in what might be regarded in an adult, as the normal range of daily reticulocyte variation.

It is evident from the reticulocyte response to phenylhydrazin that this

TABLE V

CASE 3

1932		Hgb. per cent	R.B.C. millions per cu. mm.	Retic. per cent	W.B.C. thousands per cu. mm.	P.M.N. per cent	P.M.E. per cent	P.M.B. per cent	Lymph. per cent	Monoc. per cent
Aug.	25	115	10.45		28.0					
	26				Venesection—900 c.c.					
Sept.	1	112	10.38		26.5	94	2		3	1
	2				Venesection—300 c.c.					
	2	110	9.95	1.6	14.1	93		2	4	1
	5	90	8.01	1.3	14.8	90	2	1	3	5
	6	100	8.50	1.5						
	26	105	9.93	1.3	15.4	90	1		5	4
	26				Venesection—400 c.c.					
	27	108	10.39	1.6	24.2	85	5	3	6	1
	27				X-ray to Spleen					
Oct.	28				Venesection—900 c.c.					
	29	90	7.89	1.1	28.7	91	1	2	4	2
	31	88	7.71	0.9	26.2	91	2	1	1	5
Nov.	2	84	7.66	1.3	27.0	94	1	2	2.5	0.5
	3			1.6		91	3	2	2	2
	4	88	8.09	1.2	25.0	95	1		2	2
	4				X-ray to Spleen					
	5	90	7.84	1.8	19.7	96		1	3	
	5				X-ray to Spleen					
	7	92	8.36	1.3	24.4	94			2	4
	8	88	8.17	1.1	22.5	91	3	1	3	2
	8				X-ray to Spleen					
	9	83	7.60	1.0	19.4	94	2	1	2.5	0.5
	9				X-ray to Spleen					
	10		8.09	1.5	20.0	94		3	1	2
	12	85	8.24	1.3	20.7	96	1		1	2
	14	95	7.91	1.0	17.8	89	3	3	3	2
	15	93	8.20	1.4		92	3	3		2
	16	89	7.98	1.0	20.1	95	1		4	
Dec.	5	95	8.59	1.4	15.6	94	3		2	1
	5				X-ray to Long Bones					
	6	90	8.33	0.7	17.5	91	1		3	5
	6				X-ray to Long Bones					
	7		9.10	0.7	16.1	88	5		5	2
	8	94	9.02	1.1	22.3	93		1	4	2
	8				Venesection—250 c.c.					
	9	85	8.49	1.3	19.7	88	2	1	4	5
	9				Venesection—600 c.c.					

patient's bone marrow was not in a depressed or unduly sluggish state, failing to respond to venesection. Radiation, even when applied over the long bones, did not alter the daily fluctuation in reticulocytes. There is need for more knowledge concerning response of reticulocytes to various types of marrow stimuli (hemolytic agents and marrow irritants), before we can interpret the striking difference in this patient, in the reticulocyte rise with venesection and with phenylhydrazin.

With the other three patients, the effects of venesection on the reticulocyte response were similar to Case No. 1. No noteworthy variation could be observed. In Case No. 2 the reticulocyte response to withdrawal of 850 c.c. of blood indicates that the bone marrow was not depressed or greatly inhibited by his previous exposure to radiation.

TABLE VI

CASE 4

1931		Hgb. per cent	R.B.C. millions per cu. mm.	Retic. per cent	W.B.C. thousands per cu. mm.	P.M.N. per cent	P.M.E. per cent	P.M.B. per cent	Lymph. per cent	Monoc. per cent
May	29		8.10							
June	2	92	7.14	1.6	13.8	82	1		8	7
	12				Venesection—500 c.c.					
	13			1.0						
	14			1.4						
	15			1.0						
	16		7.71	1.6	7.3	88	1		10	1
	17			0.8						
	18			0.8						
	19			0.4						
	20			1.2						
	21	84	7.27	1.4	11.5					
	21				Venesection—500 c.c.					
	23			0.8						
	24			1.7						
	25			1.8						
	26			1.0						
	27			1.4						
	28				Venesection—500 c.c.					
	29			0.6						
	30			0.8						
July	1		6.78	0.8	8.0	77	1		16	6
	2			0.4						
	3			0.0						
	5		6.68		10.3	90		1	6	3
	6			0.0						
	7			0.4						
	8			0.2						
	9	72	6.68	0.1	5.8	86			12	2

The striking effect of venesection in Case No. 3 was the almost magic relief of symptoms (dyspnea, headache, weakness). Also the response of his reticulocytes to the blood loss shows that the bone marrow of an acute, intractable polycythemia is not unduly stimulated by this procedure. It is obvious, however, that certain acute types of polycythemia cannot be satisfactorily treated by venesection alone.

Case No. 4 illustrates the inadvisability of the use of phenylhydrazin in elderly people with hypertension and polycythemia. This patient had two courses of this hemolytic agent before her venesection studies were begun. Each time the symptoms were made worse, especially weakness, paresis, mental confusion, dizziness and numbness of hands and feet. Parkes [10] suggests that the polycythemia is protective in these cases, as the work of the heart is lessened through there being more oxygen carriers in the circulation.

CONCLUSIONS

1. The results of this study indicate that venesection, used as a means of reducing the red cells and hemoglobin in polycythemia, does not increase the reticulocyte per cent above normal limits.

2. Radiation over spleen or over long bones in polycythemia, does not stimulate the bone marrow as indicated by the reticulocyte per cent. Due probably to its slow action in the reduction of the blood level, the average daily reticulocyte count was lower than following venesection.

3. In a patient with polycythemia vera, following the administration of 1.4 grams of acetyl phenylhydrazin, the reticulocyte count promptly rose to 8 per cent, gradually falling to normal over a period of 82 days.

4. The study suggests that venesection may be a useful adjunct to phenylhydrazin treatment by permitting much smaller doses of this drug to be efficient in maintaining an approximately normal blood level.

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POLYCYTHEMIA IN ASSOCIATION WITH PULMONARY DISORDERS*

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In 1919 Aldred Scott Warthin [1] published a clinical report and autopsy protocol entitled "A Case of Ayerza's Disease: Chronic Cyanosis, Dyspnea, and Erythremia, Associated with Syphilitic Arteriosclerosis of the Pulmonary Artery." Since this report, on the first case of this type to be recognized in the United States and the first to be recorded in English, increasing interest in the polycythemias secondary to chronic pulmonary disorders and to lesions of the pulmonary artery has been manifested in this country and in South America. In this particular group the essential cause of polycythemia appears to be chronic anoxemia which stimulates the bone marrow to excessive erythropoiesis.

The case which we present here is that of a high grade polycythemia, due, in the first place, to long standing bronchial asthma, chronic bronchitis and emphysema and, in the second place, to a break down of adaptation to long continued hard labor at an altitude of 10,000 feet.

Case History

(*Asthma, chronic bronchitis, and emphysema; pneumonia; peribronchial pulmonary fibrosis; polycythemia; cyanosis; failure of acclimatization to high altitude; dyspnea; hemoptysis; hematuria; increasing anoxemia and polycythemia; hypertrophy of the right ventricle; dilatation of the pulmonary artery; subacute glomerulonephritis; dependent edema; cardiac insufficiency; terminal bronchopneumonia; death; necropsy.*)

J. B., a Swedish lumber-jack, aged 45 years, was first seen May 3, 1926. At this time his chief complaints were: weakness, shortness of breath, tightness in the chest, headache, loss of appetite, loss of weight, and "pain in the stomach."

Past History: For about 25 years this patient had been a lumber-jack. Since 1920 he had worked almost uninterruptedly in Colorado at an altitude of 10,000 feet. For ten years attacks of asthma had been frequent, but following a severe attack of pneumonia in September 1921, they became much worse. In September 1925, while working at 10,000 feet altitude he noted for the first time cyanosis, increasing weakness, and shortness of breath. In January 1926, he complained of exhaustion, epigastric distress, and headache aggravated by exertion. He left camp and came to Denver (altitude 5280 ft.). After a few weeks' rest he felt better but on exertion all his symptoms returned. About April 1, 1926, attacks of asthma became more frequent, cough more troublesome and expectoration more profuse and occasionally bloody.

Physical Examination: May 3, 1926. The patient, a tall well-developed man, had slight cyanosis of the face and extremities. The tonsils were small but pus could be expressed from both sides. The teeth were in very bad condition. The fingers were clubbed. The lungs were hyper-resonant and markedly emphysematous. Many

* Read before the American College of Physicians, Montreal, February 7, 1933.
From the University of Colorado, School of Medicine, Denver.

squeaking and groaning râles were heard throughout both lungs. The heart was slightly enlarged, the pulmonic second sound was accentuated. No murmurs were heard. The abdomen was tender over the liver, which was enlarged. The spleen was not palpable. The blood pressure was 100 millimeters of mercury systolic and 80 diastolic, pulse 90, respiratory rate 20, temperature 98.6 degrees, weight 180 pounds.

The urine contained albumin 1 plus, and in the sediment a few hyaline casts and many red blood cells. The gastric analysis showed free acidity 27 degrees and total acidity 44 degrees. The Wassermann reaction was negative. The red cell count was 6,100,000, hemoglobin (Dare) 80 per cent. The white blood count was 5600; the differential count: polymorphonuclears 79 per cent, lymphocytes 18 per cent, eosinophiles 3 per cent.

Course: During the next few months the patient improved somewhat, then dropped from sight and was not seen again until December 1927. Contrary to advice he had been working for several months in a lumber camp at 10,000 feet elevation and all his former symptoms had returned with increased severity.

The physical examination now showed marked cyanosis of the face and extremities, a purplish red color of the mucous membrane of the mouth, slight edema of the feet, a faint systolic murmur over the heart and accentuation of the pulmonic second sound. The hemoglobin was 120 per cent. The red blood cell count was 7,210,000, the white blood cells 4600. The urine had a specific gravity of 1.030 and contained albumin 2 plus and a few hyaline and granular casts. The roentgenogram of the chest showed a slightly enlarged heart, an enlarged arch in the region of the pulmonary artery and marked bilateral pulmonary fibrosis. The roentgenograms of the sinuses showed clouding of the antra on both sides, especially on the left.

The electrocardiogram (figure 1) showed the usual signs of marked right ven-

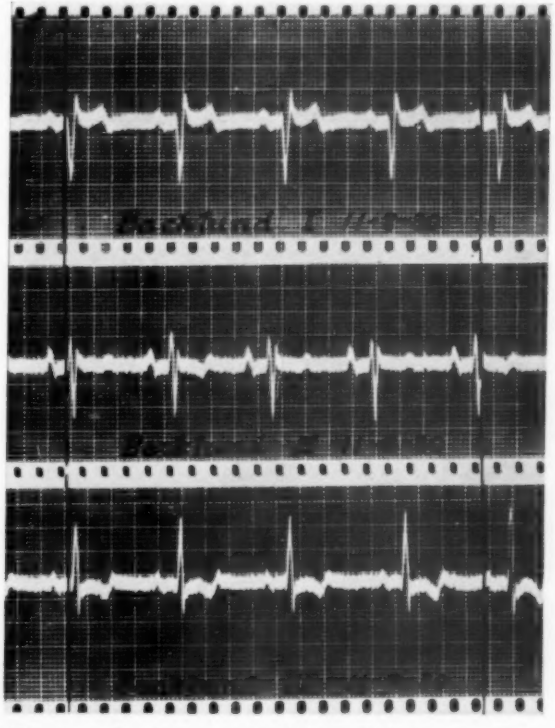


FIG. 1. Electrocardiograms showing marked right ventricular preponderance and inversion of T-waves in Leads II and III.

tricular preponderance and changes in the T-wave and ST interval in Leads II and III which during life were interpreted as indicating coronary disease. The basal metabolic rate was 60 plus. The blood sugar was 82 milligrams, urea 20 milligrams, and non-protein-nitrogen 36 milligrams per 100 cubic centimeters of blood. The Wassermann reaction was repeatedly negative. The sputum was always negative for tubercle bacilli. The patient remained in the hospital until February 1, 1928. During this time his tonsils were removed. The operation was followed by much bleeding and the red cell count dropped to 5,200,000 and hemoglobin to 100 per cent. Nine days later the count had risen to 7,270,000 and the hemoglobin to 118 per cent.

In June 1928, after working for two months in the mountains he returned in bad shape. The urine contained 4 plus albumin and many hyaline and granular casts. The red cell count was 7,290,000, hemoglobin 120 per cent and the white cell count 5600. A few weeks' treatment in bed brought some improvement.

From this time on the history of this patient up to the last few months of his life, when he was too incapacitated to work, was a repetition of the cycle of work in the mountains, relapse, hospital treatment in Denver, improvement, return to work in the mountains, relapse again. The spleen was never palpable, but the liver edge usually could be felt. The red cell count reached a maximum of 8,370,000, and cyanosis and dyspnea increased slowly but steadily. Somnolence was a conspicuous symptom.

During the last four years of his life hemoptysis always occurred shortly after his return to work in the mountains. On several occasions he had small hemorrhages from the lungs. Dyspnea and weakness increased until work was impossible and return to a lower altitude imperative. It is also significant that rest in bed in Denver without any medication whatsoever usually brought about a decided improvement in symptoms, a reduction in the size of the heart, a decrease in the red cell count and complete disappearance of albumin and casts from the urine. Figure 2 shows the change in the size of the heart brought about by six weeks' work in a lumber camp: M. R. increased from 3.2 to 4.6 centimeters, M. L. from 12 to 13.7 centimeters, L. D. from 15 to 18.2 centimeters. During the same interval the red cell count increased 40 per cent.

On June 24, 1929, he entered the Mayo Clinic.* We are indebted to Dr. George E. Brown for the privilege of using here the following notes of his examination at the Clinic. The figures for the blood volume at two examinations were 152 and 168 cubic centimeters per kilogram. The red cell count was 5,970,000, hematocrit 74 per cent (normal 45 per cent), blood viscosity 6.3, hemoglobin on admission 25 grams and on leaving 19.2 grams per 100 cubic centimeters of blood. The electrocardiogram indicated right ventricular preponderance and a slightly delayed conduction time. Roentgenographic examination of the chest showed marked fibrosis of both lungs with bronchiectasis of the left lower lobe. He was given two courses of phenylhydrazine with a rest of two weeks between courses and was discharged much improved with a red cell count of 4,800,000 and hemoglobin 80 per cent.

In March 1930, the red cell count was 8,370,000 and red cell volume by the hematocrit 82 per cent.

Dr. R. W. Danielson examined the eyes and reported: "Marked bluish redness of the conjunctiva of each eye, especially the left (with the biomicroscope the coloration is seen to be due to a myriad of dilated blood vessels rather than to hemorrhage); some pigment on the anterior capsule of the left lens from an iritis six months previously; many fine, white, round, scintillating floaters in the vitreous of the right eye; extreme tortuosity of the arteries and veins of the fundi, with increased blueness and size of the veins; increased redness of the discs, which were otherwise normal except

* Nelson W. Barker of the Mayo Clinic reported this case as one of polycythemia vera in which the pulmonary condition was either an unrelated complication or secondary to pulmonary stasis. (Barker, N. W.: Polycythemia vera and chronic pulmonary disease. Arch. Int. Med., 1931, xlvii, 94–103.)

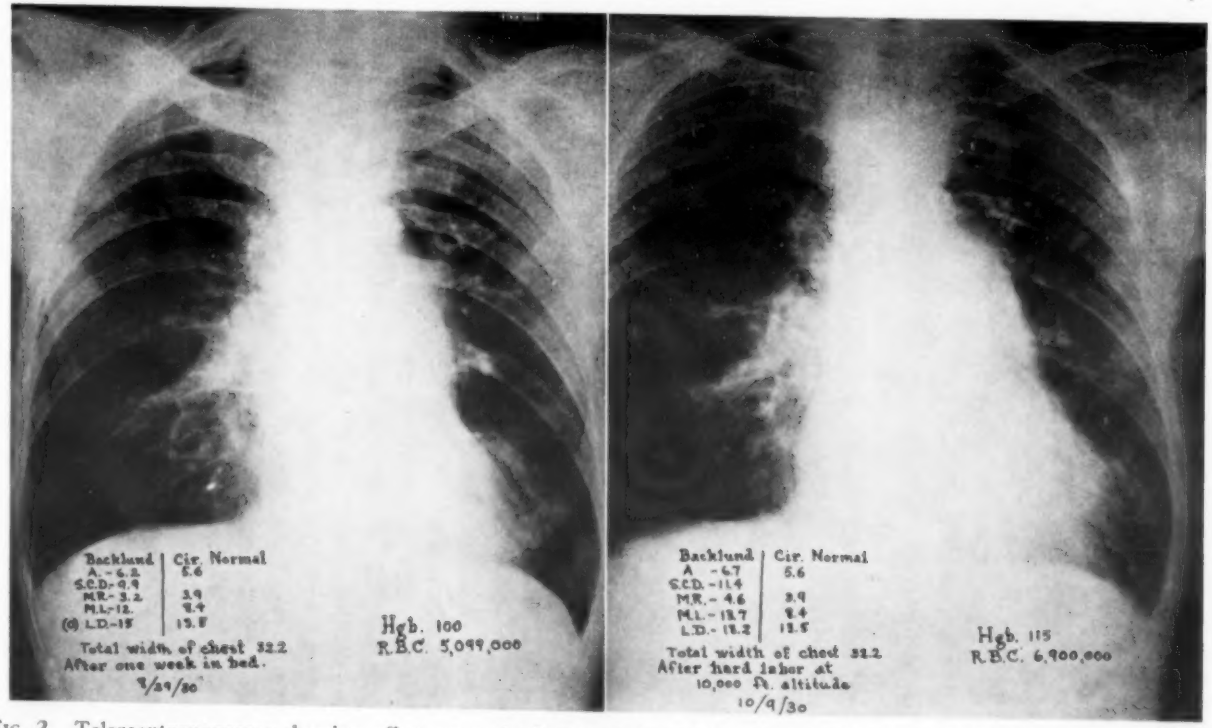


FIG. 2. Teleroentgenograms showing effect upon the heart of six weeks' labor at altitude of 10,000 feet. All dimensions are increased.

for slight blurring of the nasal side of the left disc; no exudates or hemorrhages of the retina; visual acuity (with small correction) O.D. 5/5; O.S. 5/6."

In spite of rest, change of residence to sea level, digitalis, repeated venesections, courses of phenylhydrazine and finally radiotherapy of the long bones, he went downhill more or less steadily and finally entered the Denver General Hospital in very bad condition. Both lower extremities were swollen to the hips, the hands, forearms, and genitalia were edematous. The red cell count was down to 4,680,000, hemoglobin 90 per cent. The percentages in the differential count were polymorphonuclears 48, lymphocytes 43, mononuclears 3, eosinophiles 6. Pulmonary edema increased and death came April 3, 1931, with all the signs of failure of the right side of the heart and a terminal pneumonia.

Differential Diagnosis

In the diagnosis it was necessary to consider three different conditions: (1) polycythemia vera with a pulmonary complication, (2) "Ayerza's disease," the syndrome of the "black cardiac" (cardiacos negros) or obstruction in the lesser circulation, (3) polycythemia of high altitude.

Polycythemia Vera. Since this man had a greatly increased blood volume, it is more than possible that he had a primary erythremia. Against this diagnosis it may be stated that: (1) He had two well recognized causes for anoxemia, a chronic pulmonary disorder and dys-acclimatization; (2) he was not erythrotic but intensely cyanotic; (3) a decrease in the blood count and a coincident reduction in the size of his heart usually followed rest in bed at a lower altitude, increase in the blood count and dilatation of the heart usually followed work at 10,000 feet; (4) he did not have an enlarged spleen; (5) instead of showing the leukocytosis characteristic of polycythemia vera his white blood count was always below normal; (6) the cells in the stained blood smear showed none of the qualitative changes that usually accompany polycythemia vera; (7) marked dyspnea is not part of the picture of polycythemia vera; (8) hypertrophy of the right ventricle is not a characteristic finding in polycythemia vera; (9) cyanosis, polycythemia, dyspnea, headache, nausea, loss of appetite and loss of weight, epigastric distress, and hemoptysis together present a perfect picture of chronic mountain sickness; (10) somnolence, although it occurs occasionally, has never been noted as a common symptom in polycythemia vera, but it is frequently found both in "Ayerza's disease" and in the erythremia of high altitude as described by Monge.[2] Arrillaga[3] says of the "black cardiac": "They live to sleep, fall asleep while eating and die in their sleep." It is possible that some of the reported cases in which somnolence has been recorded were really instances of "Ayerza's disease." Monge says of the victims of chronic mountain sickness: "They have an insuperable tendency to sleep."

According to Harrop[4] the respiratory symptoms in polycythemia vera are rather conspicuous. He notes a reduction in vital capacity and an increased respiratory minute volume, and states that "Dyspnea on much exertion is the rule." It will be recalled that Osler[5] in his original article in 1903 on "Chronic Cyanosis, with Polycythemia, etc.," wrote: "There is no respiratory distress with the cyanosis." Also Warthin[1] in 1919 in the fol-

lowing words emphasized the importance of dyspnea as a symptom characteristic of secondary polycythemia and not of primary erythremia: "Does a primary erythremia exist? The writer believes not, certainly not in cases showing chronic cyanosis and dyspnea. Why should a case of pure or absolute polyglobulism have either cyanosis or dyspnea? On the other hand, there is every reason why a case of chronic cyanosis and dyspnea should develop a chronic erythremia. It is most probable that all erythremias associated with cyanosis and dyspnea (with a theoretical exception of a neoplastic overformation of red cells, yet to be definitely shown to exist) are *compensatory* in nature (secondary to pulmonary sclerosis, emphysema, congenital heart lesions, chronic pulmonary diseases leading to insufficient oxygenation, increased resistance of the red cells with lessened oxygen carrying capacity, etc.)." Towards the end of the same article Warthin says: "The erythremia in Ayerza's disease is beyond question a secondary compensatory process, an increased functional activity of the bone marrow to meet the deficiency in oxygen supply due to the obstructed pulmonary circulation. It is most probable that this is the case in all forms of Vaquez' disease; certainly in all of those in which there is cyanosis and dyspnea. Neither one of these symptoms belongs to a primary erythremia; and when they are present it is certain that the erythremia is secondary."

In regard to the other listed objections to a diagnosis of polycythemia vera, it must be admitted that none of them individually is conclusive. The color of the skin and the qualitative changes in the blood in primary erythremia are variable, the spleen is not always enlarged, a reduction in the albumin of the urine after rest is not infrequent, orthostatic albuminuria has been described and, finally, Osler in 1903 noted the striking resemblance of the symptoms of this disease to mountain sickness.

The very high values (167 cubic centimeters per kilogram of body weight) for the blood volume in polycythemia vera as determined by Rowntree and Brown [6] and Brown and Giffin [7] and the low values (93 cubic centimeters per kilogram) found by Lemon [8] in cases of pulmonary emphysema and bronchitis with cyanosis indicate the great diagnostic importance of a high blood volume in separating primary erythremia from a secondary polycythemia. The high volume in our case is strong evidence in favor of polycythemia vera. Rowntree and Brown say: "We believe that increases in the blood volume to 115 or 120 cubic centimeters for each kilogram of body weight, rarely or never occur as responses of the blood to lowered oxygen tension. Whenever values in excess of these are found, we are of the opinion that they are more likely to represent the condition of true or primary polycythemia, perhaps in an early stage." This opinion is based upon the examination of a great variety of blood conditions but does not include a case of chronic failure of acclimatization similar to the *érythrémie de l'altitude* described by Carlos Monge,[2] and includes only one case of "Ayerza's disease"; this case had a blood volume of 114 cubic centimeters per kilogram of body weight although the number of erythrocytes was only

4,520,000 for each cubic millimeter of blood. In *érythrémie de l'altitude*, a malady common to the Andes where a population of six million people live at an altitude over 10,000 feet, Monge finds the blood volume very high. Unfortunately no estimations were made on these cases either by the dye or the carbon monoxide method but reliance has been placed on the hematocrit, which in an unstated number of the " indigenous acclimated " at 13,000 feet averaged 63.3 per cent. This may be compared with an average value of 62 per cent in 14 cases of polycythemia vera reported by Brown and Giffin. Monge reports one patient with very severe symptoms of dys-acclimatization who had a cell volume of 93.8 per cent. Smith, Belt, Arnold and Carrier [9] found a slight increase of the blood volume in healthy subjects during the process of adaptation to a brief sojourn at 8000 feet and in the Pikes Peak expedition of 1913, Douglas, Haldane, Henderson and Schneider [10] noted a moderate increase in blood volume. A true plethora has been found experimentally by Jaquet and Suter [11] in rabbits kept at Davos, altitude 5000 feet, and this observation has been confirmed by Guillemard and Moog [12] on rabbits at the summit of Mont Blanc. These are, however, normal responses to high altitude and it is the abnormal responses in which we are particularly interested.

In 1902 Lorrain Smith and McKisack [13] reported a case of a boy of 12 years in whom cyanosis and plethora occurred in association with tuberculous pericarditis. By the carbon monoxide method they found a blood volume of 115 cubic centimeters per kilogram body weight, which must be compared with a normal of 46 cubic centimeters per kilogram for this test. By the dye method, in which the normal is 87.7 cubic centimeters per kilogram, the value for the blood volume for this boy would certainly have been much above 125 cubic centimeters. F. Parkes Weber and Dorner [14] report a case of congenital pulmonary stenosis in which C. Gordon Douglas found by the carbon monoxide method a blood volume value of 131 cubic centimeters per kilogram. Haldane [15] says he found a similar increase in another case. In 1931 Binger [16] reported a case with a blood volume by the dye method of 123 cubic centimeters per kilogram body weight and cyanosis and polycythemia from cardiac and respiratory failure that offered much the same difficulties in diagnosis as does the one in this paper.

Apparently the pathologists are not convinced that polycythemia vera is the only condition in which a large increase in blood volume is found. The latest edition of MacCallum's " Textbook of Pathology " has this passage (page 457): " Indeed, one receives the impression from observing the amount of blood in the vessels at autopsy in cases of long-standing chronic passive congestion from cardiac lesions, that there is a great increase in its quantity." Blood volume estimations have not been made on many cases of congenital heart disease of the cyanotic group. Unfortunately they have also been omitted in a number of cases of manifest secondary polycythemia of very high grade where a high blood volume, if it ever occurs under such conditions, might have been found. It is hoped that our Spanish-American

neighbors to the south will apply the dye test to the " black cardiac " as well as to cases of *érythrémie de l'altitude.*

Although the number of determinations of blood volume in secondary polycythemia is insufficient to permit us to say how often the blood volume is increased and how high a figure may be reached, nevertheless the evidence favors the view that in this group of cases the blood volume is occasionally much increased.

" Ayerza's Disease." Our patient presented a picture closely resembling that of so-called " Ayerza's disease " or obstructive pulmonary arteriosclerosis, the essential features of which are cyanosis, dyspnea, polycythemia and right ventricular hypertrophy. To the victims of this malady, more common in South America than in the United States, Abel Ayerza,[3] Professor of Clinical Medicine at the National University of Buenos Aires, in 1901 applied the term " cardiacos negros " or " black cardiacs " to emphasize their persistent intense cyanosis and the associated cardiac disorder. Table 1

TABLE I

Summary of Essential Features

Ayerza's disease	Case: J. B.
1. A long period of symptoms referable only to the lungs.	1. Asthma 10 years, pneumonia and chronic bronchitis 5 years before onset of cyanosis.
2. A temporary erythrosis, later cyanosis months or years before signs of marked decompensation.	2. Marked cyanosis at least four years before death.
3. Dyspnea.	3. Dyspnea was an early symptom associated with asthma, chronic bronchitis and emphysema and was much aggravated after pneumonia in 1921.
4. Polycythemia.	4. Polycythemia 6 to 8.5 millions.
5. Somnolence.	5. Somnolence a very conspicuous symptom.
6. Roentgenographic signs of right ventricular hypertrophy and dilatation of the pulmonary artery.	6. Roentgenogram of heart and lungs showed right ventricular hypertrophy, dilatation of the pulmonary artery and chronic pulmonary fibrosis and emphysema.
7. Electrocardiographic signs of right ventricular preponderance.	7. The electrocardiogram confirmed the diagnosis of right ventricular hypertrophy.

illustrates the perfect correspondence between the syndrome of Ayerza and the essential features of our case. Of the nine cardinal symptoms of " Ayerza's disease " mentioned by Arrillaga,[3] viz., cyanosis, polycythemia, clubbing of the fingers, dyspnea, hemoptysis, headache, somnolence, hypercyanotic angina and angina pectoris, all in greater or less degree, were present in our case.

Polycythemia of High Altitude. The anoxemia due to the lowered oxygen tension of high altitude and the excessive demands of severe exertion in a rarefied atmosphere certainly played an important part in this case. Carlos Monge,[2] Professor of Clinical Medicine at Lima, Peru, has been a prolific writer on what he calls *érythrémie de l'altitude* and *maladie des Andes.* According to Monge, to become acclimatized it is necessary to pass through a preliminary stage of adaptation during which one manifests symptoms of

acute or subacute erythremia. If at the outset the adaptative mechanism fails quickly the result is acute mountain sickness; if the failure is prolonged over months, perhaps years, the result is chronic mountain sickness. Finally, if after acclimatization the mechanism of adaptation may break down, then one suffers from *dys-acclimatization*. In all of these instances erythremia may be found in greater or less severity. Monge states emphatically that if the biologic mechanism of adaptation fails one sees develop the symptomatology of the *maladie de Vaquez* and that this form of chronic erythremia can appear in subjects born at high altitude, in residents acclimated since infancy and even in the indigenous of pure race. The early stages are characterized chiefly by an erythremia which lasts two to ten years and by acute crises and spontaneous remissions in symptoms which are essentially those of mountain sickness, namely, cyanosis, polycythemia, dyspnea, vomiting, nose bleeds, hemoptyses, enlargement of the spleen, weakness and somnolence. On return to sea level all of these symptoms disappear. Death results from hemorrhage, pulmonary thrombosis, bronchopneumonia, cardiac insufficiency, or renal failure.

Finally Monge notes the close resemblance of *érythrémie de l'altitude* to " Ayerza's disease " from which it differs chiefly in the absence of sclerosis of the pulmonary arteries and one might add by its complete relief on return to sea level. Monge says among all these different erythremias there is one common bond, a functional disturbance of the pulmonary physiological element, the alveolus. " One should study functional respiratory syndromes as one studies those of Bright's disease." " If the functional troubles follow a chronic bronchial pneumonia or a pulmonary arteritis we have the syndrome of cyanosis and erythremia known as Ayerza's disease." The long drawn out picture of chronic mountain sickness is " absolutely analogous to maladie de Vaquez."

Return to sea level did not give complete relief to our patient, in the first place because he did not stay permanently, and, in the second place, because the pulmonary condition, asthma, chronic bronchitis, emphysema, and slowly increasing pulmonary fibrosis, had become a potent cause of anoxemia.

Monge does not explain why the mechanism of adaptation fails, but L. Ayerza, Solari and Berconsky [17] believe it to be due to a diminution in the pulmonary minute ventilation. In chronic mountain sickness there is a compensated gaseous alkalosis in contrast to " Ayerza's disease " in which there is a chronic compensated gaseous acidosis. L. Ayerza, Solari and Berconsky found the composition of the alveolar air in a " black cardiac " to be O_2 7.24 per cent, tension 51.47 mm. Hg, CO_2 9.49 per cent, tension 67.47 mm. Hg (corresponding normal figures at sea level are: O_2 14 per cent, tension 103 mm., CO_2 5 per cent, tension 40 mm.). In other words the oxygen tension of the alveolar air in this patient was about that of a normal acclimated person on top of Pikes Peak (14,110 ft.) and the percentage oxygen in the alveolar air was dangerously close to the critical level at which cardiac glycogen would be depleted and cardiac failure ensue

(Meakins [18]). A great diminution was noted in the oxygen saturation of the arterial blood which was 81.9 per cent instead of a normal of 95 per cent. The vital capacity 1540 cubic centimeters and tidal air 170 cubic centimeters were both much reduced. The minute volume ventilation of the lungs was 4.6 liters as compared with a " normal of 7 liters." The respiratory volume per kilogram of body weight was 69 cubic centimeters (normal 110 cubic centimeters) and the respiratory volume per square meter body surface was 2624 cubic centimeters (normal 4097 cubic centimeters). When this patient was tested with atmospheric air containing 3.23 per cent CO_2 his respiratory minute volume went up from 5235 to 9440 cubic centimeters and his tidal air from 186 cubic centimeters to 248 cubic centimeters. This is a distinguishing feature from ordinary emphysematous cases in which Meakins found a great tolerance for high percentages of CO_2.

The basal metabolic rate (plus 60) in our patient was very high. At the time the test was made the red cell count was 5,200,000 and the pulse rate only 68, after two weeks of digitalis. Hurtado and Monge [2] have studied the metabolic rate in visitors and residents at high altitudes and find that it varies markedly with the state of acclimatization of the individual. In the indigenous acclimated the rate is normal. In acute mountain sickness it is decidedly below normal (average minus 26 per cent in four cases of Monge), in severe *érythrémie de l'altitude* it is high (average plus 29 per cent in six cases of Hurtado with variations from plus 16 per cent to plus 67 per cent). In chronic cases of mountain sickness the basal metabolic rate increases progressively to reach a high figure in the most severe cases. In the acute forms of mountain sickness the pulse rate is very fast, in the chronic forms it is also above normal.

In the severe erythremias of high altitudes evidently a vicious circle is established. The high basal metabolic rate creates a demand for oxygen which cannot be satisfied except by return to sea level. Our man did not have manifest thyroid disease, but it is pertinent to recall that patients with hyperthyroidism and a high metabolic rate suffer more readily and more severely from anoxemia (Boothby [19]). It is equally well known that anoxemia causes the normal mammalian heart to dilate (Barcroft,[20] Katz and Long,[21] Meakins [18]). In our patient the dilatation of the heart must have been due to the combined effects of severe exertion, low oxygen pressure and high basal metabolic rate. Since normal coronaries were found at the postmortem examination, it is possible that the abnormalities in the T-wave and ST interval in the electrocardiogram were due to anoxemia. The marked clubbing of the fingers was one more sign of inefficiency of both respiratory and circulatory systems.

A high basal metabolic rate is frequently found in polycythemia vera. Minot and Buckman [22] thought the cases with the highest rate showed the greatest bone marrow activity. Brown and Giffin in tests on seven cases found the rate close to normal in four and elevated, plus 22 to plus 44, in three. They thought the higher rates were somewhat related to the higher

levels of total blood volume. In general a close relationship between the basal metabolic rate and the red cell count is not usually found.

Our conception of the evolution of the disability in this man may be summarized as follows: Long-standing bronchial asthma and emphysema produced a low grade anoxemia which was greatly aggravated by severe exertion at a high altitude. An excessive response by the bone marrow to the stimulus of chronic anoxemia induced a high grade polycythemia. The burden of pumping an increased volume of a more viscous blood through a reduced capillary bed added to the strain upon the heart. A metabolic rate rising with increased marrow activity magnified the bad effect upon the heart of an increasing anoxemia. Periodic failure of compensation coincident with the visits to high altitude furnished a forceful stimulus to erythrogenesis by a more or less rhythmic aggravation of anoxemia.

Clinical Diagnosis

Polycythemia secondary to chronic pulmonary disease and to failure of acclimatization; pulmonary arteriosclerosis; chronic bronchitis, asthma and emphysema; periodic insufficiency of the right side of the heart; hypertrophy of the right ventricle, dilatation of the pulmonary artery; chronic glomerulonephritis; chronic sinusitis; terminal pneumonia.

Pathological Report

The necropsy was performed by Dr. W. S. Dennis, pathologist at the Denver General Hospital, the microscopic sections were examined by Dr. W. C. Johnson, Professor of Pathology, University of Colorado School of Medicine. From their reports are extracted the following notes.

All the venous channels in the splanchnic region, especially the hepatic vein and portal vein, and the pulmonary artery and its branches throughout the lungs are much dilated. The heart is much enlarged, its weight 675 grams (normal 300 grams). The left ventricular wall has a maximum thickness of 20 millimeters (normal 12.5 millimeters), the right ventricular wall a maximum thickness of 14 millimeters (normal 3 to 4 millimeters). The valves and coronaries are normal. The circumference of the pulmonary artery just above the valve is 10 centimeters (normal 8 centimeters). On the intimal surface of the pulmonary artery and its primary branches are numerous subintimal yellowish patches. The aorta, except for a few yellowish plaques, closely approximates the normal. The liver weighs 1800 grams and everywhere shows marked dilatation of the venous channels. The spleen is normal in size. The kidneys are not remarkable in appearance. The bone marrow of the femur and ribs is of a deep brick red color. The lungs show moderate thickening of the pleura, consolidations in the left lower lobe and lower part of the left upper and right lower lobes, moderate emphysema and some bronchial dilatations.

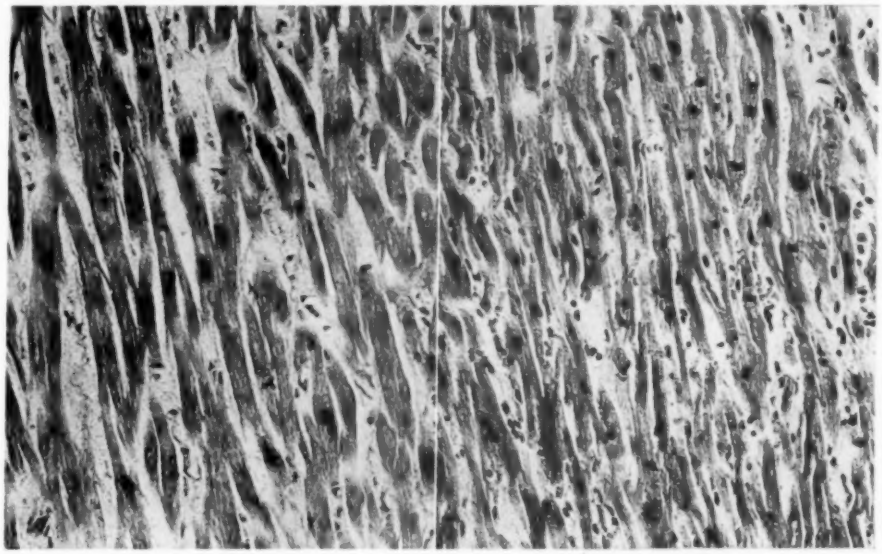
Microscopic examination shows a slight infiltration of the epicardium of the wall of the left ventricle with lymphocytes and large mononuclear cells. The muscle fibers appear normal but scattered between them is a slight infiltration with lymphocytes and large mononuclear cells. These cells are more abundant in the connective tissue septa around the blood vessels but there is no Aschoff body formation.

The muscle fibers of the wall of the right ventricle are moderately hypertrophied (figure 3). The wall of the right auricle shows slight fibrous thickening of the endocardium and the muscle fibers show moderate hypertrophy. In a few places in the endocardium and between the muscle fibers there is a slight infiltration with large mononuclear cells and lymphocytes.

Except for a slight scattered granular calcification in the media and a very slight lymphocytic and mononuclear infiltration in the adventitia, the aorta is practically normal.

The pulmonary artery shows slight thickening of the intima but it is nowhere sufficient to cause the slightest obstruction to the circulation. On the contrary even the smallest branches of the pulmonary artery appear to be dilated.

In the lungs many of the bronchi contain masses consisting of an amorphous coagulum in which are embedded leukocytes, red cells and masses of bacteria. Many



Right ventricle. Left ventricle.

FIG. 3. Sections of myocardium showing hypertrophy of muscle fibers in right ventricular wall (both photographs 160 ×).

of the organisms are cocci in chains. Other bronchi are empty. In many sections the normal columnar epithelium is replaced by low stratified epithelium. The basement membrane in most of the bronchi is very thick and hyalinized (figure 4). There is slight to marked infiltration of the bronchial walls and peribronchial tissue with lymphocytes, plasma cells, and eosinophiles. Some of the bronchi are dilated and thin-walled, and show no inflammation. The smooth muscle of the bronchial walls is slightly hypertrophied. The mouths of some of the mucous glands are dilated, but there is no sacculation as described by Macdonald.

The alveoli are mostly empty, but in one section they contain finely granular precipitate indicating edema. In some areas they are dilated and the walls appear thin. There are several patches in which the alveoli are filled with an exudate of polymorphonuclear leukocytes.

Some of the larger branches of the pulmonary artery show moderate intimal thickening, due chiefly to an increase of fibrous tissue, but there are also pale areas suggesting deposits of lipoid. A few lymphocytes and large mononuclear cells are present in the thickened intima. The media of these vessels is normal, and there is no infiltration of the adventitia or perivascular tissue. In spite of the intimal thickening there is no noticeable narrowing of the lumina of these vessels. The smaller arteries and arterioles are considerably dilated. Their walls appear thin and stretched, but otherwise normal. The lumina are empty. None of the vessels shows

thrombosis. Capillaries in the alveolar walls are not dilated, and there are very few "heart failure cells" and no other definite evidence of chronic passive congestion.

Except for a marked dilatation of the central veins of the lobules of the liver and the branches of the portal vein this organ is normal.

The spleen appears normal.

The glomeruli of the kidney are larger and more cellular than normal. The capillary endothelium and the epithelium covering the glomerular tufts are swollen. Many of the glomeruli are partly converted into hyaline material; some are completely hyalinized. Many of the capsular spaces contain small masses of hyalinized

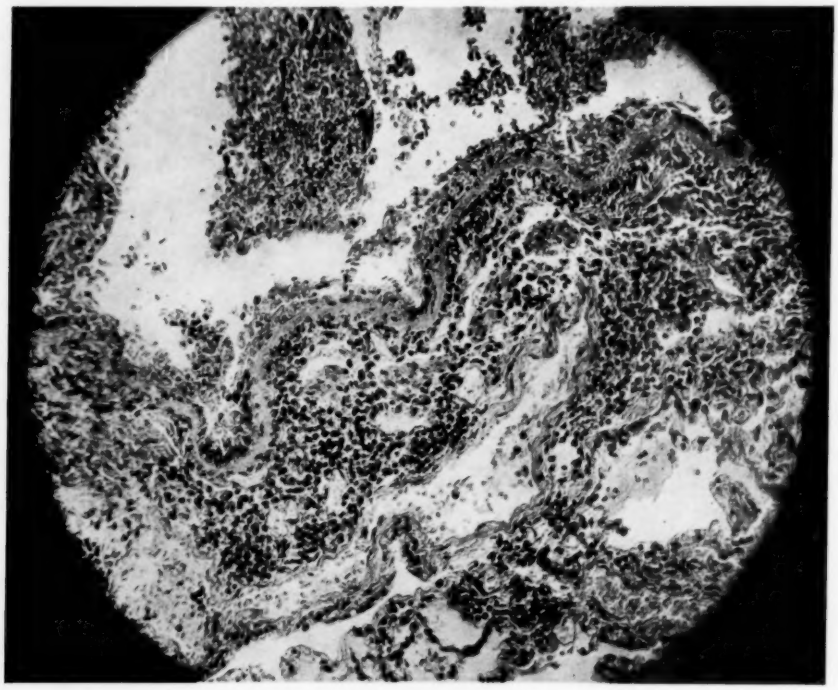


FIG. 4. Section of bronchial wall showing exudate in lumen, thickening and hyalinization of basement membrane, and cellular infiltration indicating chronic inflammation.

fibrin; a few contain small numbers of polymorphonuclear leukocytes, and some are filled with red corpuscles. Around many glomeruli the cells of the outer layer of Bowman's capsule are swollen, and frequently have proliferated to form typical epithelial crescents. Many capsular adhesions are noted. Some of the convoluted tubules are small, others are dilated and contain granular precipitate in some places mixed with red corpuscles and occasionally with polymorphonuclear leukocytes. A moderate number of small hyaline casts is present, especially in the collecting tubules. The interstitial connective tissue is slightly increased in amount, especially around the Bowman's capsules. The interstitial tissue is diffusely infiltrated with lymphocytes, plasma cells, large mononuclears and polymorphonuclear leukocytes. Some of the renal vessels show slight intimal thickening but the changes do not appear marked enough to be significant.

The bone marrow (figure 5) from the shaft of the femur is moderately congested and more cellular than normal, but the hyperplasia is not marked, and adipose tissue is abundant. Cell types do not show any distinct variation from the normal.

The pathological features of this case may be summarized as follows: The heart shows hypertrophy of the right ventricle and a slight subacute myocarditis, which may possibly be related to a streptococcus infection in the respiratory tract. The slight sclerosis of the pulmonary artery is probably related to the increased pressure in the pulmonary circulation, but there is no evidence that this sclerosis itself is responsible for any obstruction in the circulation. The branches of the pulmonary arterial system are generally dilated. The sections of the lungs show all the evidence of chronic bronchitis and emphysema and the usual picture associated with bronchial asthma. An acute but not very extensive bronchopneumonia may have been a

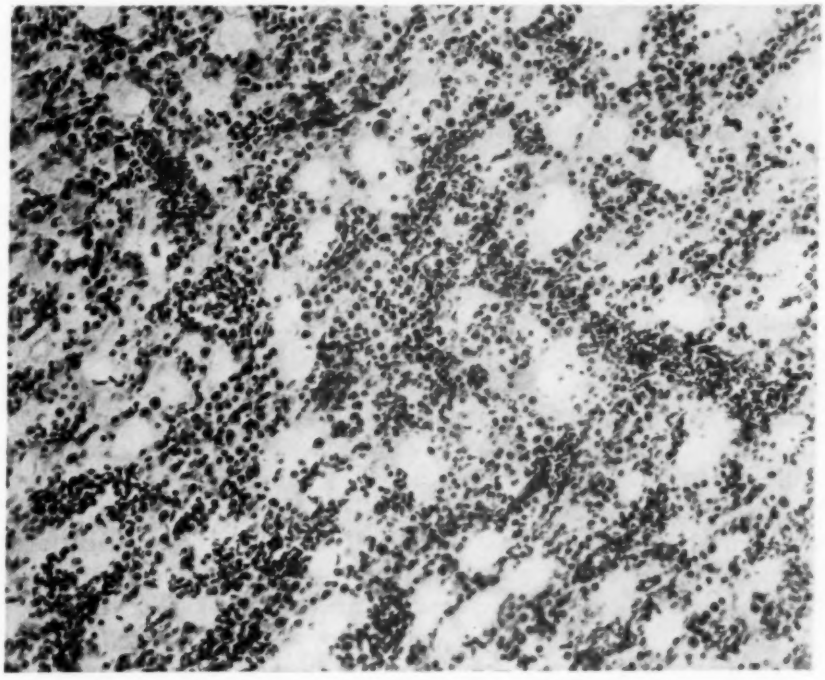


FIG. 5. Section of bone marrow from middle of shaft of femur, showing moderate hyperplasia. The sinusoids are congested.

terminal condition. The kidneys show a very marked subacute glomerulonephritis. The viscera show no evidence of chronic passive congestion. Finally the bone marrow (figure 5) of the femur is more cellular than normal, but there is nothing like the marked hyperplasia which occurs in primary erythremia.

ANATOMIC DIAGNOSIS

Chronic adhesive pleurisy, acute bronchopneumonia, chronic bronchitis, emphysema, slight hypertrophy of the left ventricle, marked hypertrophy of the right ventricle, dilatation of the pulmonary artery, slight pulmonary arteriosclerosis, subacute glomerulonephritis, moderate hyperplasia of the bone marrow.

GENERAL DISCUSSION

Current opinion holds that pulmonary arteriosclerosis is a frequent but not indispensable finding in the "black cardiac." (Warthin, Escudero,[23]

L. Ayerza, Arrillaga.) The Argentinians use the terms "cardiacos negros" and "Ayerza's disease" almost synonymously with pulmonary arteriosclerosis. The arterial lesion may be primary and affect the smaller vessels or secondary and involve the larger branches of the pulmonary artery. Originally Abel Ayerza (1901) thought the primary lesion in the black cardiac was a wide-spread pulmonary fibrosis to which the right ventricular hypertrophy was secondary. Escudero first noted (1905) the significant association of pulmonary arteriosclerosis and later (1911) suggested that syphilis might be the cause of both the prodromal pulmonary symptoms and the subsequent arterial lesions. Warthin [24] is given great credit by the Spanish-Americans for demonstrating (1917) the Spirocheta pallida in the wall and sac of an aneurysm of the pulmonary artery, but the clinical picture in this case was not that of the "black cardiac." In a subsequent paper (1919) on "A Case of Ayerza's Disease" he was unable to demonstrate the spirochete but nevertheless was convinced by microscopic study that the lesions of the pulmonary artery were syphilitic. Arrillaga formerly believed that long-continued intoxication by alcohol, or chronic disease like syphilis, tuberculosis and malaria predisposed to the localization of sclerotic lesions in the pulmonary artery, especially when chronic pulmonary processes like asthma and emphysema by increasing peripheral resistance raise the pulmonary arterial tension. He now believes that the primary lesion is a syphilitic pulmonary arteriosclerosis. Bullrich [25] reports an extremely interesting case of the cure of a typical "black cardiac" by intense antisyphilitic treatment. Arrillaga concurred in the diagnosis, which was well supported by electrocardiographic, radiologic and hematologic tests. It is quite clear that syphilis is frequently present in the "black cardiac"; it is not clear whether the arterial lesion commonly found is syphilitic or not.

Marked obstruction of the lesser circulation by thickening of the arterial wall or thrombosis has a double effect; down-stream it leads to chronic anoxemia, the clinical expression of which is cyanosis, dyspnea and polycythemia; up-stream by increasing the work of the right ventricle it leads to hypertrophy and eventual failure of the right side of the heart.

Since gas exchange is dependent upon the integrity of the alveolar-capillary wall, the capillary bed is the critical point at which obstruction to the circulation makes itself felt. Reduction in the area of the capillary bed may be due to manifest obstruction in the main channels as by pulmonary thrombosis or pulmonary arteriosclerosis, it may be due to obstruction in the small vessels as by obliterative endarteritis, or finally it may be the result of less obvious but more direct interference as in the case of pathological processes which affect the alveolar-capillary wall itself. In all instances, as in the cyanotic group of congenital cardiac defects, a portion of the blood stream is shunted away from its designated oxygenating station. Anoxemia is the result of the diversion; increased pulmonary arterial tension and right ventricular hypertrophy are the results of the obstruction.

Pulmonary arteriosclerosis of slight degree only was found in our case.

It was not sufficient to produce obstruction. In fact, from the pulmonary valve to the arterioles the pulmonary artery and all its branches were dilated and this must have lightened somewhat the labors of the right ventricle. Yet this chamber of the heart was greatly hypertrophied. In our opinion this hypertrophy was due partly to the pulmonary condition, namely, chronic adhesive pleurisy, chronic bronchitis, bronchial asthma, emphysema and peribronchial pulmonary fibrosis, and partly to the strain of hard work at high altitude. The paper of Alexander, Luten and Kountz [26] on the effect of chronic asthma and emphysema upon the heart has thrown much doubt upon the hitherto accepted idea that hypertrophy of the right ventricle is often found with bronchial asthma. These workers conclude that the heart in asthma is " rarely enlarged and often comparatively small " and suggest that a probable increase in intrathoracic pressure may decrease the filling of the heart and so reduce its burden. In sharp contrast with this study of the heart in the living asthmatic is the recent report by Ian G. Macdonald [27] on the pathological findings in eight cases of bronchial asthma collected from 3690 autopsies at the Hospital of the University of Michigan. In five of these cases death was due to cardiac failure during or following a paroxysm of bronchial asthma. Including the heart of a 13 year old girl the average thickness of the left ventricular wall in the eight cases was 18.25 millimeters, which may be compared with a normal average of 12.55 millimeters and a measurement in our case of 20 millimeters. The right ventricular wall in Macdonald's eight cases averaged 7.87 millimeters compared with a normal average of 3 to 4 millimeters and a measurement of 14 millimeters in our case. The right ventricular wall, writes Macdonald, was at least slightly thickened in every case.

The effects of emphysema, the inevitable complication of bronchial asthma, upon oxygenation and the pulmonary circulation are not easily measured but must be included in any appraisal of the influence of asthma upon the heart. In general they may be analyzed as follows: (1) A reduction in vital capacity, (2) an increase in the ratio of residual air to lung capacity, (3) a reduction in the area of the capillary bed, (4) a reduction in respiratory surface area, (5) increased tension in the lesser circulation, (6) a decrease in the assistance rendered by the thoracic and diaphragmatic movements to ventilation and to the pulmonary and general circulations. These changes lead inevitably to anoxemia and frequently to right ventricular hypertrophy.

The dilatation of the pulmonary artery and its branches may have represented the effort of the vascular system to accommodate itself to the increased blood volume (Brown and Giffin). In two cases of polycythemia vera Schreyer found the pulmonary artery much dilated and with walls only one-half as thick as normally. In neither case was the right ventricle hypertrophied. In our case, the hypertrophy of both the right auricle and the right ventricle and the dilatation of the pulmonary artery may be considered typical findings of pulmonary heart disease.

Brown and Giffin have studied renal function in eight cases of polycythemia vera. Albumin graded 1 to 3 was found in the urine in all, hyaline and granular casts in six, erythrocytes in one. The phenolsulphonphthalein elimination was slightly decreased in four cases and moderately decreased in two. They conclude that polycythemia vera exerts no marked deleterious effect directly on the kidney. Although Curschmann and Geisböck both report chronic degenerative changes in the kidneys, usually an extreme vascular fullness only is found. Turk says the renal changes are due to the "simultaneous presence of hyperemia and vascular dilatation." The glomerulonephritis in our case was probably due to a streptococcus infection of the bronchi, tonsils or sinuses. On one or two occasions, the sharp contrast between the condition of this man as he came down to Denver from camp in the high mountains and his condition two weeks later was strongly suggestive that dys-acclimatization was also an important cause of the albuminuria. Since the blood pressure was never high and examination of the blood never showed marked nitrogen retention the renal function was not seriously disturbed. Experimental work of Richards[28] and his co-workers has indicated a prompt appearance of albuminuria when the oxygen supply to the kidney is restricted. J. A. Campbell[29] has demonstrated degenerative and necrotic changes in both the liver and the kidney in certain animals for some time subjected to a low oxygen tension. Clinically, in both acute and chronic mountain sickness, evidences of serious renal embarrassment are often found. Oliguria with more or less albuminuria is commonly present, in the severe cases anuria may be found. Return to sea level brings about a remarkable diuresis within 24 hours, and usually complete disappearance of the albumin. Doubtless both the oliguria and the high cell volume (hematocrit) in the very severe cases reported by Monge are related to the gastrointestinal symptoms from which these patients often suffer. Nausea and vomiting restrict the intake of fluids and diarrhea further concentrates the blood. The red blood cells in the urine may have been due to the glomerulonephritis or to leakage from an over-filled vascular system.

The edema which became massive at the end was largely renal but partly cardiac. Alexander, Luten and Kountz included in their paper details of a postmortem examination of a chronic asthmatic who during life had dependent edema, dyspnea and cyanosis suggesting cardiac insufficiency. They found nothing unusual in the heart and therefore concluded that the edema in bronchial asthma might result from a retarded venous circulation. The increased blood viscosity in our patient must have contributed greatly to this effect.

The drop in the red cell count during the last few months of this man's life was due to three causes: (1) Residence at a lower altitude, (2) increase of plasma volume from cardio-renal edema, (3) subacute glomerulonephritis.

Conclusion

The combination of cyanosis, dyspnea, and polycythemia is the clinical expression of chronic anoxemia and the response of the bone marrow to the physiological stimulus of that anoxemia. When to this combination is added right ventricular hypertrophy, we have the syndrome of the " black cardiac " or the syndrome of Ayerza. Prolonged obstruction in the lesser circulation anywhere from the main divisions of the pulmonary artery to the pulmonary capillary bed may reproduce this clinical complex.

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A STANDARD TEST FOR MEASURING THE VARIABILITY OF BLOOD PRESSURE: ITS SIGNIFICANCE AS AN INDEX OF THE PREHYPERTENSIVE STATE *

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In health there is a balance of the various divisions of the autonomic nervous system that varies with the normal physiologic demands. It is likely that phylogenetic and anatomic factors, as well as the functional requirements of the organs have determined certain thresholds of activity of the sympathetic control of the different organs. The maintenance of cardiac rate at about 70 beats a minute, the control of surface temperature within a certain range, the activity of the sweat glands, and the control of the arterial blood pressure, illustrate these physiologic balances. Overactivity of the sympathetic and parasympathetic components of the autonomic nervous system frequently affects or produces symptoms or syndromes so distinctive as to be recognized as clinical entities, such as irritable heart or effort syndrome, or, when affecting the vasomotor nerves of the peripheral vessels, as vasospastic or vasodilating disturbances which are familiar clinical conditions. Neurogenic disturbances of the sweat glands are observed as forms of hyperhidrosis and hypohidrosis. If imbalance of the vasomotor system involves a sufficient amount of the vascular bed, alterations in the systemic blood pressure follow.

Postural hypotension represents disturbance of the sympathetic system expressed in the blood pressure, and is probably due to disease of the sympathetic nerve endings. Essential hypertension could be explained on the basis of vasomotor imbalance, with an abnormal degree of vasoconstriction. The basis of the overactivity of the different portions of the autonomic nervous system is unknown; it may be constitutional or biologic. Some disturbances of the sympathetic balance expressed as visceral neuroses are common among subjects of the constitutionally inadequate type. Psychic, emotional, or traumatic upsets may be the activating factors. The hormones that stimulate the sympathetic nerves (from the thyroid and suprarenal glands) play a part by affecting the nervous tonus. Subjects with essential hypertension are usually constitutionally adequate types, exhibiting psychic hyperirritability, with evidence of increased influence of the sympathetic nervous system, and less of the parasympathetic nervous system. The question involved in the pathogenesis of essential hypertension is whether the central or peripheral mechanism is at fault. Is there a hypersensitive vasomotor center, or are the effector tissues, the sympathetic

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nerves, the vascular tissue, or the endocrine functions responsible? Monakow and others have postulated that the vasomotor centers are hyperirritable and set at a higher level. Analogies exist in disturbances of the thermoregulatory centers in neurogenic fevers. More recent experiments by Raab throw added light on this point. He found that in cases of essential hypertension inhalation of carbon dioxide caused a rise in blood pressure several times greater than that of normal subjects. Interestingly, normal responses were found in hypertension in nephritis.

A Concept of Hypertension

There is (a) a primary or major factor, consisting of a hyperreactive sympathetic vasomotor mechanism based on constitutional abnormality or imbalance, and (b) a subsidiary factor of "wear and tear" from various environmental agents which modify or accentuate or activate the constitutional factor (table 1). It is possible that this hyperreactive mechanism

Table I

Etiology of Essential Hypertension

I. Constitutional or X factor, expressed as:
  Hypersensitive vasomotor center
  Abnormal reactor mechanism
    Arteriolar tissue
    Sympathetic nerve endings
    Endocrine.
II. Subsidiary or accelerating factors of wear and tear
  Environmental agents
  Toxic or infectious effects.

can be acquired. The aboriginal African negro does not have hypertension, but among the first and second generations of transplanted negroes, hypertension is common, and often more severe than among the native white subjects.

If there is a biologic basis which determines the subsequent development of hypertension, it should be possible theoretically to recognize this abnormality in the individual, from birth or perhaps from puberty, years before the onset of clinical hypertension. To establish this point, it was necessary to devise some type of standard stimulus whereby the pattern of reaction of the vasomotor system could be determined.

The Cold Stimulation Test

The test as employed consists in placing the subject in a recumbent position for fifteen minutes, or until the blood pressure has attained or approximated the basal level. In cases of hypertension, as long as forty-five minutes may be required. With the cuff placed on one arm, the opposite hand is placed in ice water, 4° to 5° C.; the blood pressure is taken at the end of thirty seconds and again at the end of sixty seconds. The hand is removed from the ice water and readings are taken every two minutes until the blood pressure returns to its previous basal level. The highest

reading obtained is recorded as a measure of the response. Except for a small group of subjects with hypertension the blood pressure returns to the basal level within two minutes after the hand is removed from the ice water. This reaction is independent of any significant changes in the pulse rate. There is response in both systolic and diastolic pressures, but somewhat less and more variable in the latter.

The Basis of the Reaction. It is likely that the response to cold has purely a neurogenic reflex basis, because of the speed of the reaction, which is too rapid for the intervention of any known hormonal or chemical factor. A tourniquet producing stasis of the flow of blood in the arm that is immersed fails to inhibit the reaction.

Data. Two hundred and thirty subjects have been observed. They included 69 normal subjects; 41 subjects with diseases other than of vascular type; 26 patients with localized forms of vascular disease; 76 subjects with hypertension, and 18 subjects without hypertension who seemed to be normal except that they gave abnormal reactions. The subjects were fairly equally divided as to sex.

The subjects with hypertension were grouped (on the basis of presence or absence of demonstrable organic changes in the retinal arterioles) as demonstrating organic or preorganic types of the disease. Table 2 is a

TABLE II

Responses of Blood Pressure to Cold Test

Type	Subject		Mean rise in pressure	
	Number	Age, years	Systolic	Diastolic
Normal	69	15–55	8.62 ± 0.181	8.14 ± 0.182
Hyperreactive; "normal"	18	17–40	29.33 ± 1.21	23.33 ± 1.05
Hypertension				
Organic	49	24–64	36.68 ± 1.27	24.38 ± 0.978
Preorganic	21	24–64	37.15 ± 2.07	25.04 ± 1.52
Arteriosclerosis with hypertension	6	68–91	35.00 ± 4.99	20.08 ± 0.735
Various diseases except vascular	41	18–45	8.15 ± 0.277	7.27 ± 0.192
Vascular diseases without hypertension	26	22–82	9.77 ± 0.477	8.47 ± 0.353

summary of the data obtained concerning all subjects studied. On the basis of the response of the blood pressure to cold, there were two well-defined groups: Group 1 includes subjects with minimal response to cold stimulation, and group 2 those whose response is two or more times greater. In group 1 are the normal subjects and those with other diseases than hypertension. The average response was 8.8 mm. of mercury for the systolic rise and 7.93 mm. for the diastolic rise. The range was 5 to 15 mm. systolic and 5 to 12 mm. diastolic pressure. Those subjects with increases as high as 15 mm. of mercury have been considered arbitrarily as giving maximal normal reactions. In group 2 are all patients with levels of blood pressure sufficiently elevated to cause them to be designated as having essential hypertension, and the 18 young, healthy adults of both sexes who had normal

blood pressures and no other symptoms indicative of hypertension, but whose reactions were abnormal. The mean values for the response in blood pressure were 34.5 mm. of mercury systolic and 23.2 mm. of mercury diastolic. The range was from 20 to 90 mm. in systolic pressure and from 15 to 65 mm. in diastolic pressure (figure 1). Ninety-seven per cent of

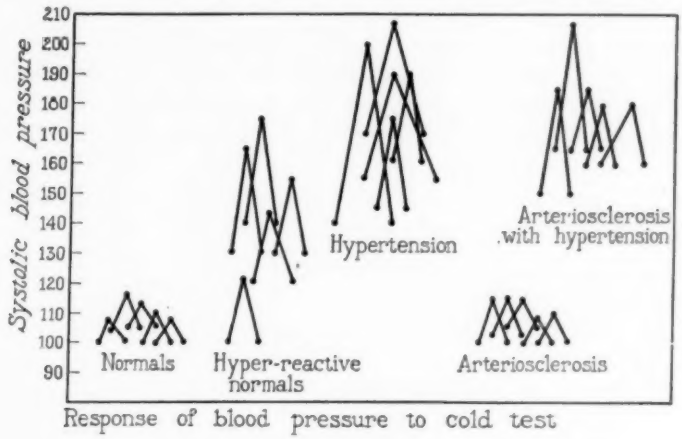

FIG. 1. Response of systolic blood pressure to cold test.

the subjects with hypertension gave a minimal response in systolic and diastolic pressure greater than the maximal response of any normal subject in group 1. With the exception of two subjects, the responses in group 2 were two or more times greater than in group 1. The two subjects whose responses were not greater than normal had the organic changes and the high fixed levels of blood pressure of the malignant form of hypertension. Basal levels were not attainable. There was no significant difference in the response in blood pressures between the preorganic and the organic forms of hypertension. In the group with hypertension there was significant correlation between the basal levels and the magnitude of the response in the systolic and diastolic pressures.

Constancy of the Reaction. Repetition of the test at short and at long intervals showed a constancy of the reaction. No conditioning effects were noted under fairly parallel conditions.

Effects of Age. We have insufficient data to allow us to state the effects of age on the reactions to cold. Among older subjects, with high grades of arteriosclerosis, responses were normal. Among older subjects with mild forms of hypertension of the arteriosclerotic type, responses were exaggerated. Further investigation of the effect of age, especially as regards infants and subjects in the later decades of life, should be carried out.

Effect of Rest. Hourly observations of blood pressure have shown that controlled mental and physical rest has a depressor effect on both the magnitude of the fluctuations and on the mean levels of systolic and diastolic pressure in cases of essential hypertension. Short periods of rest (twenty-

four to forty-eight hours) had no significant effect on the response of the blood pressure to stimulation by cold. Long periods of rest (one to two weeks) might significantly diminish the vasomotor reaction. With resumption of activity the reaction returned to its previous level.

Effect of Drugs. Derivatives of barbituric acid have a depressing effect on the reaction to cold. Sodium amytal in doses of 3 to 6 grains (0.2 to 0.4 gm.) reduced the magnitude of the reaction from 50 to 100 per cent, and the reduction endured from three to twelve hours. The effect on the blood pressure could be obtained without objective slowing of the psychic reactions (figure 2). Bromides were much less effective. Bismuth sub-

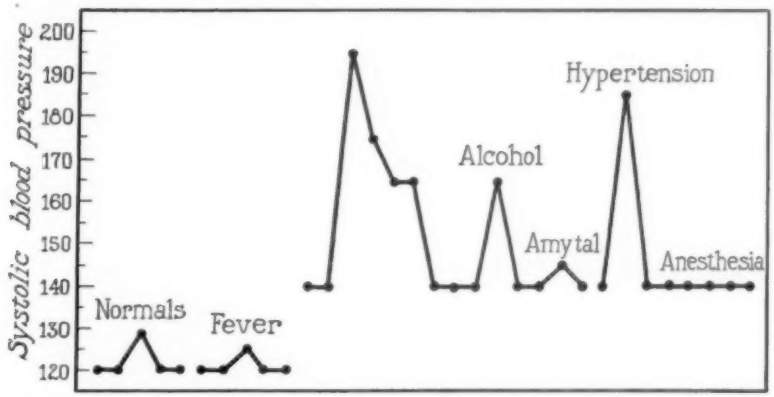

FIG. 2. Effects of different agents on the blood pressure response to cold test.

nitrate given in doses of 30 grains (2 gm.) daily for periods as long as two weeks, had no effect on the reaction. Calcium chloride given intravenously in doses of 7½ grains (0.5 gm.) gave an increased response to the cold test, and a marked delay (thirty to sixty minutes) in the return of the blood pressure to basal levels. Ethyl alcohol, given by mouth in doses of 0.5 c.c. for each kilogram of body weight, reduced the response to cold; the average decrease was 40 per cent. The duration of the decrease was from two to twelve hours. The depressor effect of alcohol was also demonstrable in the mean levels of systolic and diastolic pressure.

Effect of Anesthesia. General anesthesia caused complete obliteration of the response. Lumbar anesthesia produced a diminishing effect, roughly proportionate to the level of the anesthesia, and to the level of the systemic blood pressure. With anesthesia to the level of the nipple line, the vasomotor response was less than normal. With gradual lowering of the level of anesthesia, the vasomotor reaction increased in magnitude to the preanesthetic level (figure 3).

Effect of Quantitative Reduction of the Sympathetic Nervous System. Following either cervicothoracic or lumbar ganglionectomy, or both, on man with normal blood pressures no change was found in the vasomotor re-

sponses to cold. The response to cold of two subjects with transient hypertension was increased temporarily for several weeks after operation.

Following bilateral removal of the seventh to the twelfth or thirteenth thoracic ganglia of the dog, there was gradual reduction in the vasomotor

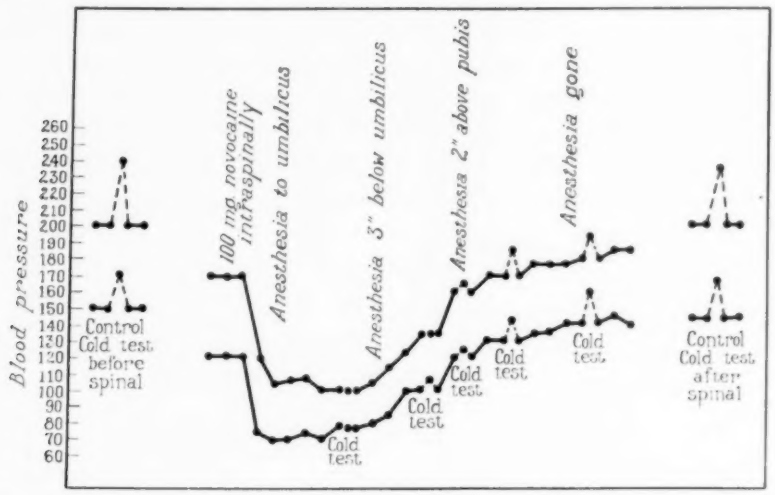

FIG. 3. Effect of spinal anesthesia on the blood pressure response to cold test.

response to cold and psychic stimulation (figure 4). In this operation the preganglionic fibers that make up the greater and lesser splanchnic nerves are removed. Splanchnic control is separated from that of the higher centers. These experiments show that with probably complete removal of the vasomotor control of the splanchnic region, there is significant decrease

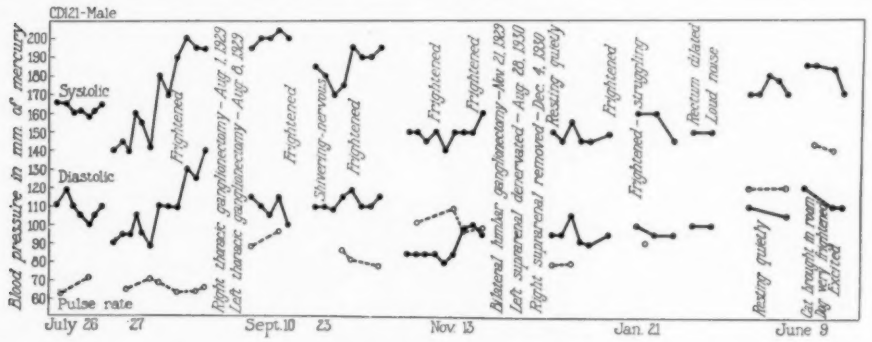

FIG. 4. Effects of thoracic sympathetic resection on variability of blood pressure in dog.

but not obliteration of response of the blood pressure to stimulation. The duration of the depressor effect is more than a year. The preoperative levels for systolic and diastolic pressure are not changed by this operation. The pressor reactions are impaired.

Part Played by the Suprarenal Glands. Following bilateral supra-

renalectomy on the dog, with life maintained by injections of cortical extract (Kendall), there was no significant decrease in the response of the blood pressure to the stimulus by cold. If the cortical extract was withheld, the vasomotor response to cold was maintained until critical levels of blood pressure supervened.

Comment

The primary etiologic factor in essential hypertension is believed to be some constitutional abnormality. The significant question in pathogenesis is whether this abnormality is of central or peripheral origin. Experimental work on the animal, with progressive reduction of the sympathetic vasomotor nerves, shows that the vasomotor reactions decrease in magnitude as larger regions of vasomotor control are eliminated. This points to a central origin. It is likely that in subjects with essential hypertension the vasomotor centers react excessively to stimuli which in the normal subject produce minimal response. A parallel is seen in Raynaud's disease, in which thermal stimulation (cold) causes excessive constriction of the peripheral vessels. In the early uncomplicated types of Raynaud's disease, the evidence indicates hypersensitively reacting vasomotor centers. In most cases of Raynaud's disease the blood pressure responses to cold are in the maximal range for normal subjects.

If the hyperreactability in essential hypertension is due to a biologic constitutional defect, theoretically its existence should be demonstrable in early life. The reaction to cold is probably of definite value in establishing this point. A few subjects have been found to react excessively before puberty. Many children of all ages should be studied and the results correlated with the type of vasomotor reactions of the parents. In this way the hereditary or familial factor could probably be determined. Our study has shown that so-called normal subjects can be grouped as hyporeactors and hyperreactors. It remains to determine the significance of the hyperreaction. There is no conclusive proof as yet that the "normal" subjects who react excessively to cold will eventually have hypertension. The belief that they may be so afflicted in the future is based on the following: (1) in the immediate ancestry of more than 75 per cent of the subjects with hyperreactions there was a history of hypertension or of apoplectic death; this figure is undoubtedly understated, for deaths from cardiac or renal causes in the families were not included, and (2) at least 98 per cent of subjects with essential hypertension have hyperreactive responses. The final proof will rest on follow-up studies carried out over a period of years.

One may question whether the hyperreactive subjects react excessively to other stimuli as well as to local application of cold. There is close parallelism, as is shown in figure 5. It is probable that all sensory and psychic stimuli produce excessive reactions in the hyperreactive subject. None has been found as effective as local application of cold. We have not discovered other diseases than essential hypertension in which there were excessive

reactions; exceptions may be found in hyperthyroidism. In cases of fever there may be lowered responses. Two subjects with Addison's disease had normal reactions. Eight subjects with intermittent systolic hypertension, associated with tachycardia recognized as "effort syndrome," have had normal reactions. In two cases of aortic insufficiency with a secondary form of systolic hypertension, normal reactions were found. In two cases of nephritis with secondary hypertension reactions were normal.

We believe that hyperreactions of the systemic blood pressure are of

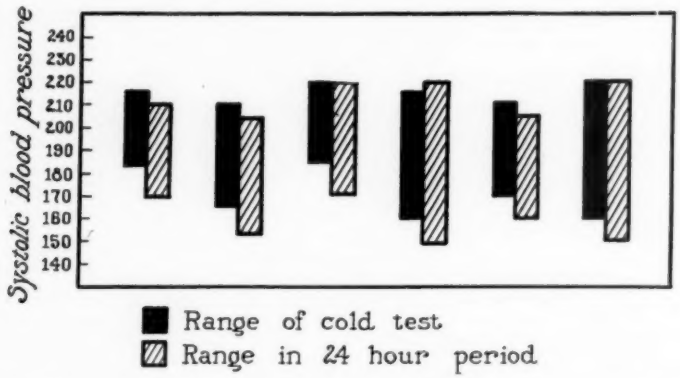

FIG. 5. Correlation of effects on the blood pressure of environmental stimuli, and stimulation by cold.

great importance in determining the vascular longevity. During the ascending period of life there is excessive intermittent tonicity of the smaller arteries associated with abnormal intermittent intravascular stress and strain. Pathologic wearing of the vascular tissue could be postulated. The first response to this excessive work on the part of the musculature of the arterioles is analogous to that occurring in the heart; that is, hypertrophy, a physiologic response. With mesial hypertrophy, true organic narrowing of the arteriolar lumen exists. With this organic narrowing of the distal arterioles, rising levels in systolic and diastolic blood pressure would be expected. At this stage the condition is recognized as clinical hypertension, probably an irreversible condition, as indicated by the lack of response to therapeutic endeavors.

The value of diagnosing hypertension in the functional, or preorganic stage of the disease is obvious. If therapeutic measures are to be of avail, they must be instituted before organic deterioration has developed. We assume that the excessive reactions are the precursors and have etiologic significance in producing the state of hypertension. If this assumption is granted, then the therapeutic viewpoint is clarified. The factors of wear and tear assume great significance and the effect of depressing the vasomotor reactions should be salutary. Regulation of occupational and avocational activity is important. A large field of experimental therapeusis is opened. Our work has just touched this interesting phase of the subject. Enough

has been done to give some hope that adequate measures of control, either medical or surgical, of the vasomotor irritability will be available in the future.

Summary

There is impressive evidence to indicate that certain subjects have a constitutional or biologic abnormality which leads to the development of essential hypertension. Demonstration of this potentiality should be possible theoretically, years before the onset of clinical degrees of high blood pressure. Subjects can be grouped as those with minimal and those with excessive responses of the systemic blood pressure to sensory and psychic stimulation. A standard test has been devised which determines this response. There is some evidence that the so-called normal subjects who exhibit this hyperreactivity will eventually suffer from hypertension unless development of this condition is forestalled.

At least 98 per cent of all subjects with hypertension of the essential form exhibit excessive reaction to local cold. Subjects with other diseases have normal or minimal reactions.* The cold test is useful in determining the efficacy of therapeutic measures to control the vasomotor irritability.

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* Briggs and Oerting (Minnesota Med., 1933, xvi, 481–486) have confirmed our studies on the cold stimulating test. They found hypertensive reactions in eight subjects with syphilis of the central nervous system. Their observation is important and needs further study.

THE DIAGNOSIS AND MEDICAL TREATMENT OF ANGINA PECTORIS*

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Angina pectoris is one of the most important and interesting conditions that we meet in the practice of medicine today. It has become increasingly so during our own generation and at present is a great and pressing challenge to us all. Our much vaunted civilization of but a few years ago has been receiving many rude shocks, and to these we may add the seemingly justified accusation that it has been responsible for much of the apparent increase in angina pectoris in our day. Certainly such apparent increase cannot be ascribed wholly to better diagnosis since our forebears for over one hundred years have known this condition well, as you will note if you read the textbooks of medicine throughout the last century. Angina pectoris is the cause today of a great deal of the disability and of many of the deaths in a community like Boston, for instance. Our own profession is riddled with it. During 1931 the deaths of a few less than 3000 physicians of the United States were recorded in the *Journal of the American Medical Association*. The causes of death were not reported in every case but in over 1000 heart disease was listed as the cause, leading the second most common cause, cerebral hemorrhage, by just 700. Heart disease occurred in 1065 and cerebral hemorrhage in 365. Pneumonia was third with 312. Tuberculosis was far down the list with only 65 deaths. The type of heart disease was specified in less than half the cases but in those so classified one-third (114) were reported as having died of angina pectoris, the other two-thirds being diagnosed as endocarditis or myocarditis save for seven cases of pericarditis. It is certain that many more cases of angina pectoris existed among those unclassified and quite probably also among those labelled simply "myocarditis." In the report of a single week, of 47 deaths in the medical profession with causes diagnosed, the heart was held responsible in 21, with angina pectoris and coronary thrombosis definitely diagnosed in eight of these. The misfortune is that most of these men were under 70 years of age; of the 21 cardiac cases only six were 70 or over; there were four in the forties and six in the fifties. It is evident that we must do something about the prevention of this dread disease, and to that most important phase of the subject I shall return at the end of this paper. It is my province now to discuss mainly the diagnosis and medical treatment of angina pectoris.

* Presented before the American College of Physicians, Montreal, Canada, February 10, 1933.

Recognition of Angina Pectoris

At the very outset the prime need is to recognize angina pectoris when we meet it and not to mistake other conditions for it. This task is generally an easy one, but errors due to carelessness are not infrequent. Let us begin with the definition and if we accept this definition, as I am confident we all do, we should not be troubled by the confusion that has occasionally, nay frequently, arisen in the past as to what is and what is not angina pectoris. Following Heberden who invented the expression, we should consider angina pectoris to mean a strangling or pressing sensation (not a stabbing pain or an ache) under the sternum occurring paroxysmally as the result of exertion, excitement, or other stimulus, and subsiding within a few minutes under the influence of rest or of nitrites. The only exceptions to this rule that may be allowed are the infrequent instances of *similar sensations* occurring *under the same circumstances* but in other parts of the chest in front or in either arm with or without radiation to the substernal region. Almost the rarest of the sites of true angina pectoris is the precordium itself in the region of the cardiac apex, that is, in the left breast. Radiation of the substernal oppression to left or to right, or to both sides, across the chest, towards or into the axillae is common, but much more so on the left side. Radiation to the left upper arm is frequent, to the left lower arm less common, and to the left hand and fingers relatively infrequent. Radiation to both arms occurs occasionally but to the right arm alone only rarely, although I have met an instance of an oppressive sensation limited to the right wrist, the cause of which was coronary disease. Radiation to the neck in the middle or on either side is infrequently encountered, to the jaws still less often, and to the back very rarely. I cannot recall a single instance in which the sensation radiated downwards into the abdomen or legs, although it may sometimes start in the epigastrium and penetrate upward under the sternum. As a rule the more severe the substernal oppression the more extensive the radiation, but there are frequent exceptions to this rule, and in some cases a very severe strangling sensation remains closely located in a small area under the middle of the sternum. When radiation does occur, the sense of oppression becomes modified to a burning, tingling, or numb feeling the further it radiates. Finally, it should be observed that among the stimuli that may produce angina pectoris there is in rare cases paroxysmal tachycardia or paroxysmal auricular fibrillation with rapid ventricular rate, the oppression in the form of the so-called status anginosus persisting while the tachycardia persists, just as it would do if there were persistence of other factors like exercise or excitement; this association of angina pectoris with paroxysmal tachycardia or paroxysmal auricular fibrillation has been recently called to attention because of the likelihood of confusing it with coronary thrombosis. The middle-aged or elderly male is most commonly the victim of angina pectoris, usually following much strenuous living.

Symptoms other than the substernal oppression, that have sometimes

been referred to as a part of angina pectoris are a sense of impending dissolution and faintness. Neither of these has been at all a common accompaniment of angina pectoris in my experience. Actual syncope (syncope anginosa) is rare. *Angina pectoris sine dolore,* a paradox in itself, is a term that has been used to describe feelings or symptoms that are assumed to occur as the result of acute coronary insufficiency in the place of the characteristic oppression or its variations. The term is very unsatisfactory and confusing and should be dropped. In contrast to coronary thrombosis which may be painless angina pectoris is a symptom and if that symptom is absent we cannot call other symptoms such as giddiness or an all-gone feeling angina pectoris even though coronary disease is present. When syncope complicates angina pectoris the oppressive feeling comes first.

Types and Causes of Angina Pectoris

The fundamental types or causes of angina pectoris may be briefly considered now. Although the last word has as yet by no means been said with reference to the pathogenesis or mechanism of angina pectoris, we have advanced far enough to have a much clearer idea of the situation than was possible a generation ago when the controversy was at its height between those who supported the aortic origin of angina pectoris and those who supported its coronary origin. Four weighty arguments that have almost conclusively proved that the symptom is due to coronary insufficiency are: first, that angina pectoris and proved coronary occlusion give the same kind and location of pain, second, that angina pectoris is often complicated by coronary thrombosis or indeed may appear for the first time after coronary thrombosis, third, that those cases of luetic aortitis with narrowing of the mouths of the coronary arteries are the ones that show angina pectoris while those cases of luetic aortitis who fail to show coronary mouth involvement even though the aortic lesions may be much more extensive, perhaps with actual aneurysmal sacs, do not have angina pectoris, and fourth, that constriction of the coronary artery in the dog produces pain while distension of the aorta does not. Thus we start with the premise that angina pectoris is caused by temporary coronary insufficiency. Equally important and even more conclusive is the evidence that the symptom occurs most readily in individuals with nervous hypersensitivity. It is practically unknown in lethargic persons and in full-blooded negroes, no matter how much coronary disease may be present in them. This very fact accounts for one of our greatest difficulties in the diagnosis of angina pectoris; the persons who are apt to have symptoms of various sorts easily produced are very likely to have angina pectoris also, although often the relatively sheltered lives that many of these individuals lead doubtless protect them from the strains that usually precipitate angina pectoris. With these introductory remarks we may attempt a simple classification of the types of angina pectoris as follows; the first two groups are quite certain, the last three probable or possible:

1. Coronary arterial sclerosis. A loss of elasticity with or without

much calcification and narrowing of the coronary arteries is the most common lesion in angina pectoris. In such cases the pain is doubtless induced by the improper functioning of the coronary circulation when there is extra demand on the myocardium; the myocardium in its turn is often thickened as the result of chronic hypertension or other strain and so requires more blood than before. The predisposing factors which impose the extra load are mainly, exertion, excitement, and eating, but include also anemia and tachycardia, the latter induced by thyrotoxicosis or occurring paroxysmally.

2. Coronary mouth occlusion by luetic aortitis or in a very rare case by ball valve obstruction from vegetations on the aortic valve may cause angina pectoris with such provocation as outlined under coronary sclerosis or indeed with less provocation.

3. Coronary arterial vasoconstriction, a vascular spasm, has been suggested as an occasional or frequent cause of angina pectoris, perhaps in the smaller vessels superimposed on sclerosis of the larger trunks. It has not been proved but may help to explain the attacks of angina pectoris occurring in hypersensitive individuals who suffer from hypertensive storms with relief of the angina pectoris on such occasions not directly related in time to the drop in blood pressure. However, in such cases further factors like aortic regurgitation or thyrotoxicosis may be present, and always or almost always structural changes in the coronary arteries themselves.

4. Marked aortic regurgitation and marked aortic stenosis have been found in a few cases of angina pectoris with no evidence of coronary disease clinically, but as yet there has not been clear postmortem evidence that the coronaries or their mouths are entirely normal. Also it has been in a part of this very group consisting of young people with marked aortic regurgitation that angina pectoris has occurred with hypertensive storms perhaps attended by coronary vasoconstriction. It is possible that, but open to some question whether, the diminished coronary blood flow that exists with marked aortic regurgitation or marked aortic stenosis can be sufficient basis for angina pectoris of effort.

5. Finally, we have recently encountered an infant who on such exertion as taking its milk would grow pale and cry out as if in pain and who after death from collapse at the age of four months showed the rare anomaly of malposition of the left coronary artery which arose from the pulmonary artery instead of the aorta. The electrocardiogram of this child showed typical coronary T-waves. The heart was enlarged and before death we had made a tentative diagnosis of congenital idiopathic hypertrophy.

In concluding these comments concerning the types of angina pectoris it should be added that certain conditions like severe anemia and thyrotoxicosis favor the onset of angina pectoris but do not cause it in a perfectly sound heart so far as we are aware. Extremely rare cases in which pressure on the coronaries from without gives rise to pain have been referred to as possible but I have not myself encountered any.

Diagnosis of Angina Pectoris

The diagnosis of angina pectoris is wholly dependent on the patient's history unless one happens to observe a typical attack and note its relief by rest or nitrites. The sensation of the patient is the entire clue; all else is merely suggestive or corroborative of the diagnosis of coronary disease. Since it is obvious that this is so and since the diagnosis is a most important one, it behooves every one of us to take personally the detailed history given by the patient himself, and not to delegate the history taking to a relatively untrained medical student, assistant, or secretary. It is far better to delegate the physical examination than the history if for any exceptional reason the entire examination cannot be made by oneself. It is failure to observe this simple precaution of taking a careful detailed history of symptoms that has caused most of the mistakes of omission or commission in the diagnosis of angina pectoris. It is probably neither wise nor conclusive to give epinephrine as a diagnostic test.

There may or may not be complications with angina pectoris. The commonest are hypertension, cardiac enlargement, coronary thrombosis, and nervousness. Less common, but not infrequent, are aortic valvular disease, luetic aortitis, diabetes, and well marked generalized arteriosclerosis. Rare are congestive failure, auricular fibrillation, and mitral valvular disease. About one-fifth of all the cases show no abnormalities of the circulation on physical examination, roentgen-ray study, or electrocardiography. A few show no abnormalities except for intraventricular block or coronary T-waves in the electrocardiogram; these are common enough to make it wise to take electrocardiograms of men or women over 40 years old in all insurance examinations for large sums. A few instances have been recorded of transient changes in the electrocardiogram during attacks of angina pectoris; the opportunity to obtain such records is, however, infrequent and the finding is not a constant one.

The differential diagnosis of angina pectoris is generally a simple matter. This symptom should not be confused with the dull prolonged heartache or sharp stabbing knife-like or "pins and needles" pains of neurocirculatory asthenia or of big pounding hearts in nervous persons, even though such pain may be referred occasionally to the shoulder or down the left arm as a numbness. It is this kind of pain that is most often called pseudo- or false or secondary angina pectoris; such terminology is misleading. These aching or stabbing pains are a variety of *dolor pectoris* but not of *angina pectoris* as Heberden himself clearly recognized. In fact, angina pectoris is often described by the victim as not being pain at all, while the stabbing and aching sensations are always described as pain or dolor. There are four clues to the differentiation of these pains, which are largely of nervous origin, from angina pectoris: (1) their site (left breast), (2) their character (described above), (3) sensitiveness of the left breast to touch or pressure, and (4) other symptoms of neurocirculatory asthenia like sighing, faintness, and exhaustion. Angina pectoris itself may be slight or severe, but

it is always angina pectoris and not pseudo-angina pectoris. It is, however, important to remember that both angina pectoris and neurocirculatory asthenia may coexist in the same patient; the unravelling of such a case is of great interest and importance.

The next most common confusion in the differential diagnosis in the past has been between angina pectoris and coronary thrombosis. Although the clear separation clinically has been made only in the past decade, it is now easy except for rare borderline cases which need further study. The pain of coronary thrombosis is exactly like that of angina pectoris except that it is much more prolonged, lasting hours instead of minutes, and often, but not always, it is more severe.

So-called aortic pain probably occurs only when the aortic wall is seriously involved, and then it is quite likely to be due as much, or more, to the result of pressure of the dilated aorta, especially if there is a saccular aneurysm, on adjacent structures as to the lesions in the aortic wall itself. True aortic pain in clear cut cases is quite different from angina pectoris. It consists of a prolonged heavy ache, sometimes likened to a throbbing toothache, and often lasting hours or days at a time, unrelieved by nitrites and at times requiring morphine repeatedly, or paravertebral alcohol injection. It is commonly located in the region of the upper sternum and base of the neck especially to the right of the midline and often in the right shoulder or arm also, probably because the common site of extensive involvement of the aorta is in its ascending portion and is directed to the right. An interesting type of aortic disease that has recently attracted our attention because of the possibility of its confusion with coronary thrombosis, rather than with angina pectoris, is dissecting aneurysm of the aorta. Severe prolonged substernal pain, and usually upper back pain too, occur when the aortic wall is split, and sudden death may ensue hours or days later when the dissecting aneurysm ruptures into the pericardium or pleura.

Pericardial and pleural pain is easily differentiated from angina pectoris by its prolonged character, its usual aggravation by respiration, its association with an acute infection, and by the presence in most cases of a friction rub.

Finally, we come to four causes of pain in the upper chest not due to involvement of the cardiovascular apparatus itself. They are, first, trouble with the bones, joints, muscles, or bursae of the thoracic cage, spine, or arms due to muscle strain, arthritis, or bursitis. The differentiation of this type of pain from angina pectoris is simple in nearly every case because of its usual location in other than the substernal region, its aching character and prolonged duration, and its aggravation by certain movements or positions of the thorax or arms. The other three causes of chest pain simulating angina are all subdiaphragmatic in origin. They are peptic ulcer, gall-bladder disease, and gaseous distension of the gastrointestinal tract, particularly of the stomach and colon. The pain of peptic ulcer often radiates up under the sternum and may extend out to the left shoulder and

into the left arm or into both arms but it is burning rather than strangling in nature, it lasts more than a few minutes as a rule, and it is relieved by food. Gall-bladder pain rarely need be confused with angina pectoris; its maximal site is usually in the right upper quadrant of the abdomen or in the epigastrium; when it is referred to the chest it goes to the right shoulder or back in most cases; it is colicky in nature, often associated with vomiting, and it lasts for more than a few minutes. When it is of a character suggestive of heart pain it is coronary thrombosis rather than angina pectoris from which the gall-bladder disease must be differentiated. It must be recognized, however, that gall-stones and coronary disease not infrequently occur together in the same patient. The final condition, namely gaseous distension of stomach or colon, has for a long time been very confusing so far as the heart is concerned and has been in part responsible for the traditional misnomer of acute indigestion for angina pectoris and coronary thrombosis. However, this confusion should melt away in the light of our present knowledge and of careful study of individual cases. It is true that angina pectoris may be precipitated or its occurrence favored by distension of the stomach with food and air and by the increased metabolism that results from active digestion, it is also true that in some people constipation and distension of colon with gas and feces favor the occurrence of coronary pain, and finally it is true that relief of an individual attack of angina pectoris may or may not be attended by the belching of gas from the stomach, but these are all simply associated conditions, do not themselves give rise to typical substernal oppression which might be confused with angina pectoris, and are more likely to be absent than present. Their importance has been greatly exaggerated except as they may prove to be exciting or aggravating factors. Many people belch gas frequently and have persistent bloating of stomach and colon without angina pectoris and many people have angina pectoris without any gastrointestinal symptoms at all.

In leaving the differential diagnosis of angina pectoris I need simply add that there are a few other infrequent causes of chest pain easily distinguished from angina pectoris because of the character, duration, or site of the pain; such causes are herpes zoster, tabes dorsalis, mediastinal or bronchial tumors, and subdiaphragmatic hernias.

Treatment of Angina Pectoris

The *medical treatment* of angina pectoris is of great importance, contrary to the fatalistic belief of many doctors and laymen who are so impressed by the uncertainty of life in the cases of those afflicted that they consider it unnecessary to take any particular measures. Of immediate concern, of course, is the treatment of the attack itself and the traditional measures are well known to you all: rest and nitroglycerine or amyl nitrite. Standing or sitting stock still is of prime importance and alone may permit the attack quickly to subside. Recumbency is to be avoided; in fact when

the attacks come on at night in bed, the quickest relief is usually obtained by getting up at once and standing by the bedside. Some patients tell of their ability to walk off the attack; this is usually, I believe, impossible, and probably always dangerous. Inhalation of amyl nitrite from a pearl quickly dissipates the oppression through its vasodilating effect. Its strength, however, is rather overpowering for some people, it is sometimes a bother to break the pearl, and it is rather expensive for frequent use. Nitroglycerine in tablet form in the dosage of 1/200 grain crushed and dissolved in the mouth acts almost as quickly as does amyl nitrite, is more easily taken, and is less expensive. The larger doses of 1/100 and 1/50 of a grain of nitroglycerine should be used cautiously for not only may they give rise to unpleasant symptoms of excessive flushing of the face and throbbing and congestion in the head, but in sensitive individuals they may cause faintness, collapse, and actual syncope, as we have discovered in four of our own patients in the past two years. If no nitrites are available whisky and brandy may be used for relief of an attack but their action is rather slow. Morphine should not be resorted to except when the distress is maintained as with paroxysmal tachycardia or coronary thrombosis. A few patients have told me that certain exercises like deep breathing, contraction of the abdominal muscles, and belching of gas seem to help to abolish the substernal oppression of angina pectoris.

To prevent attacks of angina pectoris when this symptom has once appeared and to treat the underlying coronary disease, strict rules of rest and exercise and diet should be laid down. Medicinal therapy is far less important except under the following three circumstances: if luetic aortitis is present, careful but thorough antiluetic therapy should be instituted beginning with mercury or bismuth and potassium iodide and alternating such a course with one consisting of the administration of neoarsphenamine; if severe anemia is present it should be treated as indicated with liver extract or iron; if paroxysmal tachycardia occurs, quinidine sulfate rations may help. Vasodilating and sedative drugs given at intervals seem to help some individuals, especially the bromides or barbital for nervousness, and they may be tried more or less routinely; often, however, they have no beneficial effect, and if so they need not be continued after a trial course. These drugs include theobromine, theophylline ethylene diamine, the nitrites, pancreatic and muscle extracts, carbon dioxide inhalations, barbital compounds, and the bromides. There is one very useful procedure that may be adopted in rather severe cases, to help render life less miserable and more active; that is to use a nitrite like nitroglycerine prophylactically at intervals as needed to permit the accomplishment of necessary activity such as dressing in the morning, going to stool, and starting off to work. Such a measure should, however, be regarded as a privilege and not abused. It has proved helpful in a number of my patients and in some has been used advantageously instead of the alternative procedures of complete invalidism or of paravertebral alcohol injections. Similarly sodium nitrite or better still

erythrol tetranitrate may be given at night to help to prevent the angina of decubitus. The erythrol is sometimes too strong and causes headaches; if it does, the usual dose of 1/2 grain may be reduced to 1/4 grain. Finally, alcohol in the form of whisky or brandy may be used prophylactically at intervals; it is effective in some cases but it is probably not a good habit to establish and it is expensive. Digitalis has not proved of value in my cases; in fact in some it has apparently aggravated the trouble.

Of all therapeutic procedures for angina pectoris, rest is the most important and the most neglected. It is well to advise at the very beginning *saturation with rest* covering at least a few weeks or probably more beneficially a few months. Certainly angina pectoris is just as important as many other things like nervous prostration and tuberculosis that are treated by prolonged rest, and it is almost always benefited though usually not completely cured by such rest. Nature is striving to improve the coronary circulatory deficiency and the best way to help this natural tendency is to get rid of physical and nervous strain at least for the time being. Sometimes angina pectoris disappears altogether even without absolute rest but it is more likely to do so with rest. Nervous tension which is an important part of the background of angina pectoris is also benefited by rest and perhaps even more than is the coronary disease itself. Then after the initial saturation with rest, rations of rest periodically are invaluable; such rations may consist of weekends in bed regularly, a long weekend away from home every fortnight, a week of rest once a month, or a fortnight of rest every three months. There are various ways to work this out. Meanwhile there should also be a daily rest, for example, a lazy hour after luncheon, and bedtime should be early. To have breakfast in bed sometimes helps. For each case the doctor should prescribe the amount and time of rest and exercise as carefully as he would prescribe a medicine. But with all this, great care must be taken to avoid the establishment of a neurosis which may be more difficult to treat than the angina pectoris itself. A healthy optimistic attitude of mind must be constantly maintained by the doctor and inculcated in the patient; psychotherapy of this sort is invaluable.

Exercise within the patient's reserve is advisable. It is good to maintain proper tone of the general musculature of the body, to have the diaphragm in good working order, and to keep the brain and the bowels in condition by physical exercise, of which walking and mild calisthenics are the best for the cardiac patient. Golf is permissible if it is carried on in a leisurely manner and not on hilly courses, and if it does not cause angina pectoris. Fishing is often ideal. Most of the more strenuous games and sports are to be discountenanced. After every meal there should be at least one-half hour and preferably one hour of rest in the sitting position.

Excitement in contrast to exercise should be studiously avoided by patients with angina pectoris. It is unwise to take unnecessary risks, and to court excitement is such a risk. Contact with crowds may be included here. Anger is dangerous. Hurry and worry induce a nervous element that may be the last straw.

There are certain measures for the improvement of the general health that sometimes help also in reducing the frequency and severity of angina pectoris and even in rare cases in abolishing it altogether for the time being. Included in these measures, all of which are worthy of consideration, are the clearing up of focal infections like infected teeth, the correction of surgical conditions that give rise to distress or irritation such as gall-stones or hernias, the control of constipation, and the use of methods of physical therapy like carbon dioxide baths, massage, and perhaps diathermy. So far as I know these measures have only an indirect influence on angina pectoris, but if that influence is favorable it does not much matter whether it is direct or indirect. The regulation of habits and the institution of physical therapy under the pleasant and restful surroundings of some health resorts and spas are undoubtedly of benefit to some patients with angina pectoris, and periodic resort to such places once or twice a year for a few weeks may be well worth while. Caution should be exercised, however, against doing too much in the way of surgery, dentistry, or physical therapy in a short space of time.

Finally, we come to diet and climate. There is no special diet to be recommended in the treatment of angina pectoris, but there are simple rules. Hearty meals, food difficult to digest or noted as favoring the accumulation of gas, dinner at night, and stimulating drinks like strong coffee had best be avoided. As already advised there should be a rest period after meals. The use of alcoholic beverages need not be denied but heart symptoms will often follow any excess in this direction. Wine and beer perhaps are helpful in reducing the nervous tension in some people with angina pectoris. The low incidence of coronary disease in chronic alcoholism is, however, scarcely enough of a benefit to counterbalance the disagreeable character of the lives of such alcoholics and their cirrhotic livers. Most of my own angina pectoris patients have not used alcohol; of one group of 331 cases 194 or 59 per cent have been abstainers. However, one of the heaviest drinkers in my practice was one of those most seriously affected by angina pectoris in frequency and severity; the only possible benefits that he may have derived from his habit were that he lived a carefree life (he fortunately was able to) and that he survived 20 years of the angina pectoris.

Tobacco is probably a different matter. I am inclined to believe that it is wise to advise its omission in angina pectoris since it does in some individuals prepare the ground for attacks. Most patients claim that smoking makes little or no difference in influencing the frequency or severity of their angina pectoris. Of a series of 331 angina pectoris patients of my own 87 or 26 per cent smoked to excess, 100 or 30 per cent used tobacco moderately, and 144 or 44 per cent were non-smokers.

Little need be said about climate except that a mild climate winter and summer favors longevity in angina pectoris; it is important to avoid heat but much more important to avoid the cold.

Roentgen-ray treatment of angina pectoris has been proposed and tried

during the past few years, by radiation of the posterior nerve roots and the chain of sympathetic ganglia. Little has come of it to date.

For intractable angina pectoris in carefully selected cases paravertebral alcohol injections and nerve section have proved of value. These methods of treatment are dealt with in the paper by Dr. James C. White.

It has become my firm conviction, as the years of my experience with angina pectoris go by, that much may be done to make the lot of the victim of angina pectoris easier and happier, and to prolong his life. Many of the catastrophes of sudden death in angina pectoris that we read about so often in the newspapers are avoidable; some are not. We should do all we can to keep alive valuable members of society for the sake of their families, friends, and communities, and it is unfortunately just these valuable people who are apt to suffer from angina pectoris.

Finally, in closing let me quote from an early English translation published in 1542 of the "Regiment of Helthe" of the University of Salerno, the medical school of note which flourished in Southern Italy in the Middle Ages. Whether angina pectoris was one of the evil conditions to be prevented by following these rules we cannot say but it is likely that it was. "The first doctrine is that he that desireth helth of body must eschew and avoyde great charges, thought, and care. . . . The second doctrine is to eschewe anger. . . . The thyrde doctryne is to eate and drynke sobrely. . . . The fourth doctrine is to make a light souper." The fifth doctrine advises exercise. Some there be, however, who would prefer to follow Edna St. Vincent Millay's poem where it is written

> I burn my candle at both ends.
> It will not last the night.
> But ah my foes, and oh my friends,
> It gives a lovely light.

Between the extremes of complete disregard of health and excess of prudence there lies a middle course which should avoid presenile angina pectoris and yet allow one to enjoy a useful and a happy life.

EXPERIMENTAL AND CLINICAL STUDIES IN THE SURGICAL TREATMENT OF ANGINA PECTORIS*

By JAMES C. WHITE, M.D., *Boston, Massachusetts*

FOLLOWING François-Franck's[1] suggestion that the pain of angina pectoris could be relieved surgically, Jonnesco,[2] Leriche,[3] Danielopolu,[4] and Hofer[5] abroad, and Coffey and Brown[6] in this country have developed operations for resecting part or all of the known cardiac nerves in the neck. These structures consist of the superior, middle, and inferior cervical sympathetic ganglia and their cardiac branches; also the depressor nerve when it is present as a separate branch of the vagus. All of these procedures have produced strikingly successful results in some cases, but none has been uniformly successful. As a result there has been complete confusion concerning the physiology of cardiac pain and its pathways to the central nervous system. This problem was bound to remain insoluble until an operative procedure could be devised which would give consistently successful results, or until a method could be found of studying cardiac pain in animals. Mandl's[7] and Swetlow's[8] method of paravertebral injection of the sympathetic ganglia is now promising to fulfill the first requisite, in that attacks of angina pectoris can be definitely stopped by successful injections of the upper thoracic sympathetic ganglia. The second requisite has been fulfilled by a recent discovery of Sutton and Lueth[9] which has made possible the experimental production of cardiac pain in dogs.

Using this method, which consists of the temporary occlusion of the descending branch of the left coronary artery, White, Atkins, and Garrey[10] have tested the efficiency of the different possible neurosurgical operations for denervating the heart in a series of 29 dogs.

In four control animals it was found that occluding the flow of blood in the descending branch of the left coronary artery for periods of from 15 to 30 seconds produced uniform and definite signs of discomfort in each dog.† It was impossible to maintain the occlusion for over 30 seconds without causing unnecessary suffering on the part of the animals. Division of both vagi or of the upper five pairs of intercostal nerves had no effect on the pain. (Table 1.) In seven dogs in which one or both stellate ganglia were removed evidences of pain were still present, as was also the case in two dogs after resection of the left sympathetic trunk from the stellate down through the fourth thoracic ganglion. But when this last named procedure was performed on both sides, no evidence of pain could be

* Read before the American College of Physicians at Montreal, February 10, 1933. From the Cardiac Clinic and the Surgical Services of the Massachusetts General Hospital.

† For want of a better word to describe the characteristic reaction to experimental coronary occlusion of this duration, the phenomena described above will be referred to hereafter as evidence of cardiac pain. But it is most important to emphasize that none of these animals was ever permitted to suffer acutely.

TABLE I

Efficiency of Various Neuro-Surgical Procedures in Interruption of Cardiac Pain Pathways in the Dog

	Dog	Neuro-Surgical Operation	Reaction to Occlusion of Coronary Artery
Controls	1	—	+++
	2	—	+++
	3	—	+++
	4	—	+++
	5	Stellate Ganglionectomy (Left)	+++
	5	" through D_4 (Left)	+
	7	" " D_5 (Left)	+++
	8	Bilateral Stellate Ganglionectomy	++
	9	" " "	++
	10	" " "	++
	11	" " "	+
	12	" " "	++
	13	" " "	++
	14	" " " through D_4	0
	15	Posterior Root Section, D_3–D_7 (Left)	+++
	16	" " " D_1–D_4 (Left)	+
	17	" " " D_1–D_4 (Right & Left)	+++
	18	Anterior and Posterior Root Section, D_1–D_5 (Right & Left)	0
	19	Posterior Root Section, D_1–D_5 (Right & Left)	0
	20	Intercostal Nerves, D_1–D_5 (Right & Left)	+++
	21	Division of Vagi (Right & Left)	+++

elicited. Two dogs in which the upper five posterior spinal roots were cut bilaterally also showed no evidence of pain. Protocols and kymographic tracings of these experiments are given in the recent paper referred to above.[10]

From these experiments it is apparent that only removal of the upper thoracic ganglia or section of the corresponding posterior spinal roots can cut all the afferent connections between the heart and the central nervous system. There must therefore be direct connections between the second, third, fourth, and possibly the fifth thoracic ganglia and the heart which cannot be reached by any of the classical operations in the neck.

Observation of the motor response of the heart to stimulation also shows direct connections between the thoracic ganglia below the stellate and the heart. While faradic stimulation of the stellate ganglia causes an increase of heart rate up to 80 per cent, stimulation of the second and third thoracic ganglia after resection of the stellates causes an acceleration of heart rate up to 58 per cent. (Table 2.) In some instances there was an even greater increase in pulse rate on stimulating the second and third thoracic ganglia than on stimulation of the stellates. These observations corroborate the work of Cannon, Lewis, and Britton.[11]

Previous operators have felt that removal of the cervical sympathetic ganglia with their superior, middle, and inferior cardiac nerves was sufficient to denervate the heart. This was a natural supposition, as no other sympathetic cardiac nerves were known five years ago. That 40 per cent

TABLE II

Increase in Heart Rate on Sympathetic Trunk Stimulation

Dog	Stellate	D_1 & D_2
22	11% Left	—
23	78% Right	—
24	80% Right	—
25	75% Right	—
26	88% Right	7% Left
27	20% Left	55% Left
28	10% Right	28% Left
29	4% Left	58% Right

Faradic stimulation of stellate or of 2nd and 3rd thoracic ganglia after section of the vag or their paralysis with atropine. The figures recorded above represent the greatest percentage increases in heart rate which were obtained. In Dog 25, the spinal cord had been previously transected in its third cervical segment and both adrenal glands had been removed, in order to eliminate the possibility of any reflex stimulation of the brain centers or the adrenal glands.

of these operations were failures is probably accounted for on the basis that surgeons neglected these direct thoracic connections which we have described running between the heart and the sympathetic ganglia below the level of the stellates. (Figure 1.) These connections have recently been shown in the anatomical dissections of Jonnesco and Enarchesco,[12] Braeucker,[13] and Kuntz and Morehouse.[14] Their physiological importance in conducting both afferent and efferent impulses is shown in our experiments.

Clinical results based on these anatomical and physiological findings are as follows: Where the sympathetic rami and ganglia were blocked with alcohol in 28 cases of severe angina pectoris, 57.6 per cent of cases were entirely relieved of their attacks on the injected side, another 23.1 per cent were greatly benefited, 7.7 per cent were but slightly improved, and only 11.6 per cent were failures. All of these cases were carefully selected by Dr. Paul Dudley White as being the most severe or obstinate cases of angina pectoris coming to the clinic. Milder cases which could be maintained in even relative comfort on a medical regime were never treated surgically. None was refused on account of being too sick, although several would have been impossible risks for any form of nerve resection. All were totally unable to perform any kind of work, and several were having many attacks while at rest in bed. Many had had previous coronary thrombosis. In spite of this, good results were achieved in 80 per cent of the cases treated by alcohol injection, as against 58 per cent reported for the several varieties of cervical sympathectomy.* Each case of failure appears to have been due to faulty injection. Outside of one death from bronchopneumonia in a moribund woman of 85, no serious complications have resulted from these injections, but a varying degree of alcoholic neuritis of the intercostal nerves is a frequent and at times a most annoying complaint after injection therapy.

In four cases where the sympathetic ganglia have been resected from the

* Three further patients with aneurysm of the aortic arch were entirely relieved of their pain by injection of only the first and second thoracic ganglia.[15]

For the technic of performing paravertebral alcohol injection, see previous papers by the writer.[16, 17, 18]

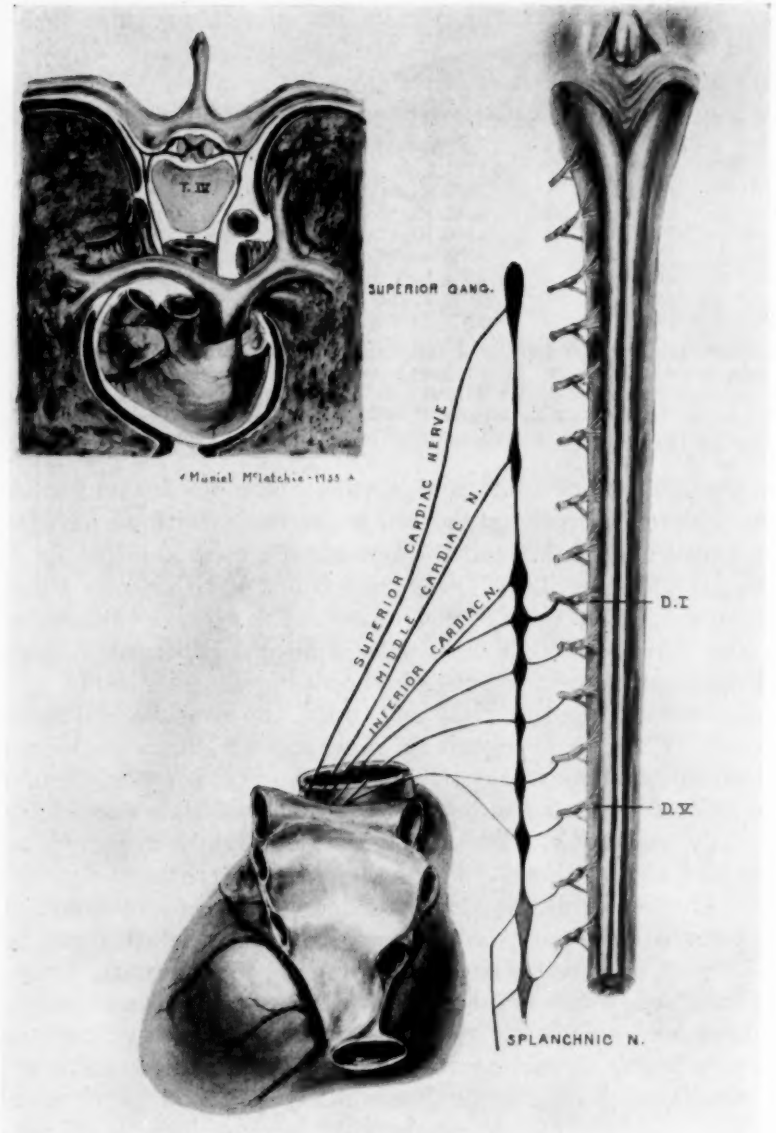

FIG. 1. Diagrammatic representation of the sympathetic nerve supply to the heart depicted in heavy black. The lower, direct thoracic nerves, the importance of which is emphasized in this article, are shown running from the upper five thoracic ganglia to the posterior cardiac plexus. It appears from our work that these nerves carry both sensory and motor impulses. The middle and inferior cardiac nerves have long been known to conduct both afferent and efferent stimuli, but the superior cardiac nerve is supposed to be purely motor. It is obvious from this diagram why the removal of the cervical sympathetic ganglia frequently fails to relieve angina pectoris. It can readily be appreciated that all cardiac connections can only be blocked by either:

1. Resection of the upper thoracic sympathetic ganglia.
2. Blocking the white sympathetic rami which unite these structures with the intercostal nerves.
3. Cutting the corresponding posterior spinal roots.

The spinal cord is viewed from the back. Only the white communicant rami are shown, as these alone are concerned with afferent and efferent impulses to the heart. In order to simplify the drawing, the latter organ is shown displaced to the left.

The insert gives a transverse section view of these structures at the fourth thoracic level.

first through the fourth thoracic segments, relief has been complete in three. The fourth continues to have mild attacks in the arm area, presumably transmitted through the upper portion of the stellate ganglion, which was not excised. Of even greater significance in favor of the correctness of this theory of the anatomical pathways of cardiac pain, is the fact that two of these cases who died subsequently of coronary occlusion had intense right-sided pain in the attack, without any discomfort on the operated left side.

Since the completion of our animal investigations, we have not had a suitable case for posterior root section, but of three cases where this operation has been utilized by Davis [19] and by Cone [20] since this work has been completed, all have been relieved.

Table 3 shows in summarized form the type of case, the method of treatment, and the result obtained in our series of 32 injections or operations for angina pectoris.

We believe that these findings point to a rational conception of the cardiac pain pathways and that their application should promise more satisfactory results in the surgical treatment of angina pectoris. It is our personal opinion that the effectiveness of these procedures is due to blocking the afferent pain pathways from the heart. We are aware, however, that this point has not been fully proved and that some writers believe that the benefit of operation is due to interrupting cardio-pressor reflexes. Our experimental findings demonstrate that it is equally important in either event, to use a thoracic, rather than a cervical approach. Paravertebral alcohol injection is the safest method at our disposal, but fails to give satisfactory relief in a fifth of the cases because of its technical difficulty. Resection of the upper thoracic ganglia or section of the corresponding posterior spinal roots appears to offer nearly certain relief, but the mortality from these radical procedures is certain to be appreciable. On this account we plan to employ alcohol injection on patients with angina pectoris who fail to obtain sufficient relief from medical measures. In the small percentage of cases which fail to obtain adequate relief, the resulting fibrosis of the parietal pleura will make ganglionectomy a difficult procedure, but it will in no way interfere with the subsequent exposure and sectioning of the posterior roots in suitable cases.

Summary

1. Pain from the heart and the ascending arch of the aorta is conveyed to the sympathetic trunk by fibers running in: (a) the middle and inferior cardiac nerves to the corresponding cervical sympathetic ganglia, (b) recently discovered nerves which run directly across the mediastinum from the posterior cardiac plexus to the upper thoracic sympathetic ganglia.

The painful stimuli thence enter the spinal nerves through the white communicant rami. As there are no white rami in the cervical region, all

TABLE III

Patients Treated Surgically for Angina Pectoris at the Massachusetts General Hospital, 1927–1933

28 Cases Treated by Paravertebral Alcohol Injections:

No.	Age	Diagnosis	Treatment	Relief	Duration	Status at Last Report
1	54	Syphilitic aortitis, aortic regurgitation, hypertension, angina pectoris; confined to bed; angina decubitus, 15 attacks daily. Much milder attacks on right.	D_1–D_5 Left 2/27. D_3–D_7 Right 3/28.	100% 0	6 yrs.	Unable to work, but fairly comfortable. Partial decompensation. Patient is in better condition today than before his first injection.
2	60	Hypertensive and arteriosclerotic heart disease, aortic regurgitation, angina pectoris, previous attack of coronary occlusion, slight congestive failure.	D_2–D_6 Left 5/27. Re-injection: D_1–D_3 6/27.	60%	To death, 7 mos.	Able to resume light work until sudden death undoubtedly from coronary thrombosis or angina pectoris, on Feb. 8, 1928; no autopsy.
3	53	Arteriosclerotic heart disease, hypertension, angina pectoris at rest.	D_1–D_5 Left 6/27.	25%	To death, 2¼ yrs.	Up and about, quietly active, appearing good health but with moderate angina pectoris. Died of empyema.
4	54	Moderate arteriosclerosis and enlarged heart; angina pectoris; incapacitated.	D_1–D_5 Left 7/27.	100%	To last report, 2½ yrs.	In fair health, but still has right-sided angina pectoris (mild); resumed work as truck-driver for 3 months, but is too short of breath now.
5	56	Arteriosclerotic heart disease, hypertension, myocardial insufficiency, previous coronary thrombosis.	D_1–D_5 Left 8/27.	40%	To death, 4 mos.	Died suddenly on Jan. 9, 1928, undoubtedly of coronary thrombosis or angina pectoris; no autopsy.
6	52	Hypertensive heart disease, aortic regurgitation, angina pectoris at rest.	D_1–D_5 Left 11/27.	100%	To last report, 2¼ yrs.	Comfortable and able to do light work, 5 mos.
7	58	Arteriosclerotic heart disease, hypertension, angina pectoris.	D_1–D_5 Right 3/28.	65%	To last report, 5 mos.	Fairly comfortable and has resumed light work.
8	68	Arteriosclerotic heart disease, hypertension, angina pectoris, previous coronary thrombosis.	D_1–D_5 Left 4/28.	50%	To death, 10 mos.	Comfortable, mild angina pectoris daily, but able to be quietly up and about. Died of coronary thrombosis.

TABLE III—*Continued*

No.	Age	Diagnosis	Treatment	Relief	Duration	Status at Last Report
9	47	Hypertension, arteriosclerosis, coronary thrombosis, angina pectoris; confined to bed.	D_1–D_5 Left 9/28.	100%	To death, 2 mos.	Died of myocardial failure with right-sided angina pectoris on Nov. 4, 1928.
10	51	Arteriosclerotic heart disease, coronary thrombosis, angina pectoris, morphinism.	D_1–D_5 Left 9/28.	—	No pain to death, 3 weeks.	Five days later another attack of coronary thrombosis; died Oct. 4; died too soon to judge.
11	56	Hypertensive and arteriosclerotic heart disease. Angina on exertion.	D_1–D_3 Left 6/29.	100% 50%	4 mos. To death, 22 mos.	Worked for 4 mos., then a stroke. Attacks in arms after that.
12	57	Hypertensive and arteriosclerotic heart disease. Angina on exertion. Coronary thrombosis.	D_1–D_4 Left 10/29.	90% 50%	4 mos. 3¼ yrs.	Still able to do light work.
13	56	Arteriosclerotic heart disease, coronary thrombosis. Angina on exertion.	D_1–D_3 Left 10/29.	100% 60%	1 yr. 3¼ yrs.	Still practising medicine.
14	54	Arteriosclerotic heart disease, coronary thrombosis, decompensation, angina decubitus.	D_1–D_4 Left 10/29.	100%	?	Followed only 2 weeks.
15	49	Arteriosclerotic heart disease, angina on any exertion.	D_1–D_3 Left 10/29.	90% 50%	3 mos. 17 mos.	Returned to work.
16	57	Arteriosclerotic heart disease, angina on exertion.	D_1–D_4 Left 11/29.	0		Continues as before treatment.
17	52	Syphilitic heart disease, aortitis, angina decubitus.	D_1–D_4 Left 11/29.	0		Continues as before treatment.
18	70	Arteriosclerotic heart disease, aortic stenosis, hypertension, angina pectoris.	D_1–D_5 Left 11/29.	100%	To last report, 26 mos.	Continues pain free and can climb two flights of stairs without oppression.

TABLE III—*Continued*

No.	Age	Diagnosis	Treatment	Relief	Duration	Status at Last Report
19	64	Arteriosclerotic heart disease, coronary occlusion, angina pectoris for 8 years, attacks increasing, come on slightest exertion.	D_1–D_4 Right 3/30.	100%	To last report, 27 mos.	Doing light housework.
20	63	Arteriosclerosis, hypertensive heart disease, aortic regurgitation, angina pectoris.	D_1–D_5 Left 4/30.	50%	To last report, 8 mos.	Returned to work as lawyer.
21	43	Mitral stenosis with severe pain in precordium and partial decompensation.	D_1–D_5 Left 1/31.	100%	To death, 10 mos.	Unable to work because of dyspnea. Died during operation on mitral valve at another hospital.
22	59	Hypertensive heart disease, angina pectoris.	D_1–D_4 Left 2/31.	75%	To last report, 24 mos.	Reports mild pain in left arm, none in chest.
23	53	Rheumatic heart disease, coronary occlusion, angina pectoris.	D_1–D_2 Left 9/31. D_2–D_5 Left 10/31.	Pain in arm stopped. 100%	To death, 4 mos.	Died of decompensation and without recurrence of angina pectoris.
24	64	Arteriosclerotic heart disease, coronary occlusion, angina pectoris.	D_1–D_4 Left 9/31.	90%	15 mos.	Unable to work on account of dyspnea.
25	85	Arteriosclerotic heart disease, angina pectoris, advanced cerebral arteriosclerosis. Patient exhausted by severity and frequency of attacks. Injection performed with realization that patient was moribund.	D_1–D_2 Right 10/31.	Apparently complete.		Died of bronchopneumonia 2 days later.
26	61	Arteriosclerotic heart disease, moderate hypertension, coronary occlusion, angina pectoris.	D_1–D_4 Left 12/31.	60%	1 yr.	Very mild attacks after injection. Died of cardiac failure without pain.
27	60	Arteriosclerotic heart disease, hypertension, angina pectoris.	D_1–D_3 Left 9/32.	—	4 mos.	Insufficient ganglia injected with only slight relief. Should have D_4 and D_5 injected.

TABLE III—*Continued*

TABLE III—*Continued*

No.	Age	Diagnosis	Treatment	Relief	Duration	Status at Last Report
28	54	Arteriosclerotic heart disease and coronary occlusion. Constant precordial pain with frequent severe attacks of angina pectoris. Patient exhausted with suffering.	D_2–D_5 Left 1/33.	100%	—	Only 3 weeks have elapsed since injection, but the relief of his constant pain and of the dread of his severe attacks, together with the resultant ability to sleep and eat, have produced a dramatic transformation. He appears to have gained a new lease on life.
4 Cases Treated by Thoracic Ganglionectomy:						
29	20	Rheumatic heart disease and aortic regurgitation. Angina pectoris up to 15 times a day. Severe precordial pain on left, mild on right.	D_1–D_3 Left 2/5/29.	100%	To death.	Mild right-sided attacks constituted a good warning signal. Died of cardiac decompensation and coronary occlusion 8 months later. Attack of agonizing pain in right precordium lasted 3 hours before death. No pain on left.
30	29	Syphilitic aortitis with closure of mouths of coronary arteries. Angina pectoris.	D_1–D_3 Left 9/19/29.	100%	To death.	Excellent postoperative convalescence. On 13th day developed symptoms of coronary occlusion. Died after 4 hours of terrific pain in right precordium, none on left side. Autopsy: coronary occlusion.
31	60	Arteriosclerotic heart disease and angina pectoris.	D_1–D_3 Left 10/1/29.	90%	To date.	Mild anginal attacks on unoperated right side. She still has some radiation to left arm, but gets along comfortably on medical measures which did not give her sufficient relief before operation.
32	62	Arteriosclerotic heart disease with coronary thrombosis leading to angina pectoris.	D_1–D_3 Left 10/1/29.	100%	To death.	This patient had no money, felt he had to work, and demanded being subjected to operation with knowledge of its greater risk in order to be sure of relief. He developed postoperative pneumonia, but was discharged in 3 weeks. No further pain. One month later died painlessly of coronary thrombosis. Autopsy showed occlusion of both coronary arteries.

Note: The percentage of relief was estimated at follow-up examinations in the Cardiac Clinic by Dr. Paul D. White. These figures apply only to the side injected or operated upon, as the unoperated side was never affected. The duration of improvement is dated to last report.

Six of the alcohol injections summarized above were done by Dr. W. J. Mixter, the remaining ones by Dr. J. C. White.

The thoracic ganglionectomies were performed by Drs. W. J. Mixter, A. W. Allen, and J. C. White.

pain sensation referred over the cervical sympathetic trunk must descend to the upper thoracic ganglia before it can reach the spinal cord. Therefore impulses traversing either of these routes converge on the upper thoracic sympathetic ganglia to reach the spinal cord via their white rami communicantes and the corresponding posterior spinal roots.

Pain referred to the left or right precordium or the arm enters the cord only on the same side.

The vagus nerve carries no important pain fibers from the heart.

Desensitizing the skin areas to which cardiac pain is referred by section of intercostal nerves does not give permanent relief of cardiac pain.

2. Operations on the cervical sympathetic trunk, even if they include the stellate ganglia, cannot interrupt all the pathways of cardiac pain.

3. The upper thoracic sympathetic ganglia or their communicant rami or the posterior roots of the corresponding spinal nerves are the logical points at which to interrupt painful stimuli from the heart.

4. These anatomical and physiological premises have been put to the test in 32 cases. In each case where we have been sure of a successful interruption of the above mentioned structures, angina pectoris has disappeared.

5. Paravertebral alcohol injection is difficult technically because of the depth of the nerves and the small areas sclerosed by the alcohol. However, it is the safest method that we have and its results are far better than the old forms of cervical sympathectomy.

6. The upper thoracic sympathetic ganglia have been resected in four cases, with striking relief of pain on the operated side. We believe, however, that this is too severe an operation for the average patient suffering from angina pectoris.

7. We believe that the best surgical procedure consists of first attempting to block the thoracic sympathetic nerves with alcohol. The cases which fail to obtain satisfactory relief, provided they are reasonably good surgical risks, can finally be subjected to section of the posterior spinal roots.

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MANAGEMENT OF EDEMA *

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THE DISCOVERY that certain forms of edema are readily influenced by diet and by other therapeutic measures is one of the important contributions to clinical medicine of the past decade.

A certain small amount of fluid normally exists in the intercellular spaces of the body. When it accumulates in quantity it is called edema. Edema may be local or general, hidden or grossly manifest. Fluid may accumulate in the serous cavities as a part of the general process with no essential difference in mechanism. Edema may occur in clinical conditions that are apparently quite dissimilar—in inflammation, allergic states, anemia, malnutrition, nephritis and cardiac failure. The mode of production probably varies greatly with each type. Undoubtedly many factors are involved. Of these, increased hydrostatic pressure and consequent increased capillary permeability, disturbances of osmotic pressure, and variations in the acid-base balance of the serum and tissues are best known and lend themselves most readily to therapeutic manipulation.

It is interesting to note that Richard Bright, in his writings which appeared in the Guy's Hospital Reports from 1827 to 1843, recognized that the albuminuria of nephritis occurred at the expense of serum protein, and implied that dropsy was aggravated by blood letting—then a common therapeutic procedure—due to the depletion of blood proteins. In 1903 Widal in France and Strauss in Germany observed the marked effect that the administration or withdrawal of salt in the diet had upon edema. Widal's classical case in which he was able to increase or reduce edema at will by the administration or withdrawal of salt is well known. These observations appear to be the beginning of the modern clinical study of edema. It is to be regretted that the significance of the observations of these clinicians remained so long unappreciated.

The clinical and experimental study of the mechanism and management of edema has been tremendously accelerated in recent years. At the present time various phases of the problem are being studied in many clinics. Undoubtedly with the development of new concepts concerning the mechanism of edema, the details of management will change greatly during the next few years. However, from the great mass of recent experimental studies many observations of practical therapeutic value have emerged, concerning which there can be no reasonable doubt. In formulating practical procedures for the control of edema, advantage should be taken of such established facts. A few only may be mentioned at this time. An excellent

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review of the subject with an extensive bibliography has recently been published by Peters.[1]

1. *The state of the kidneys,* save under exceptional conditions, has little to do with the mechanism which determines the retention of fluid in the body. In acute nephritis a hyperemic plethora with retention both of salt and water may occur, conceivably solely the result of kidney damage. In chronic and subacute diseases the functional reserve of the kidneys, however, is so great that sufficient renal function is usually preserved to carry on adequate renal work even in the presence of gross kidney damage.

2. *The restriction of water intake,* save under unusual conditions, does not materially contribute to the relief of edema. In fact, edema may increase or decrease independently of the water intake. While the ingestion of inordinate amounts of water may induce edema, water taken in ordinary amounts serves as an excellent diuretic. The radical restriction of fluid intake, therefore, is not included in the ideal diuretic regimen.

3. *In the presence of failing circulation* with increased hydrostatic and filtration pressure, edema appears to be due not only to mechanical interference in circulation but also, in part at least, to interference with peripheral cellular physiologic processes such as the $O–CO_2$ exchange. Therefore, therapeutic measures directed toward improvement of the circulatory status, such as bed rest, cardiac stimulants (digitalis and strophanthus) and oxygen therapy constitute an important part of the regimen directed toward the relief of edema of this type.

4. *The serum proteins* appear of *first* importance in maintaining the osmotic equilibrium as between the cellular elements and fluids of the body. The importance of maintaining a normal serum protein level in the face of disease is, I believe, not sufficiently realized. The physiologic integrity of the tissues is largely dependent upon the availability at all times of an adequate supply of serum proteins. The normal level of 5 or 6 grams per cent is readily maintained under normal conditions by a daily ration containing one gram protein per kilo of body weight. Depletion of serum protein occurs clinically as a result of protein restriction in diet, protein waste as in albuminuria, or as a result of disturbed metabolic processes. Since it is well established that the concentration of the electrolytes of the serum varies inversely with the concentration of the proteins, depletion of serum protein automatically raises the concentration of the total base. When serum proteins are depleted below a level of 3 or 4 grams per cent, edema may appear as a compensatory process; hydration of the body and a great increase in the salt content of the serum result, as reported by Leiter,[2] Barker and Kirk,[3] and Shelburne and Egloff.[4] Disturbances of the protein content of the serum may, therefore, determine the state of hydration of the body. Efforts to maintain an adequate protein concentration in the serum should include the prescription of a diet containing sufficient protein to cover inordinate consumption of protein in metabolic diseases such as hyperthyroidism and diabetes, and loss by way of the kidneys as in albuminuria. Save in the

presence of nitrogen retention this may be accomplished without difficulty. Blood transfusions or the intravenous injection of acacia as recently recommended by Hartmann, Senn, Nelson and Perley,[5] may serve as temporary substitutes.

5. *Disturbances of the acid-base equilibrium* of the serum are probably of *second* importance in determining the state of hydration of the body; they lend themselves readily to therapeutic manipulation.

In this connection it should be remembered that *sodium* makes up more than 90 per cent of the total base of the blood serum and extracellular fluids; that potassium, calcium and the other bases, essential as they are for normal growth and cellular physiologic processes, are, from the point of view of the acid-base balance, of negligible importance since they represent not more than 10 per cent of the total base of the extra-cellular fluid. Therefore, as far as practical therapeutic procedures are concerned, what is said of total base applies almost equally well for sodium in the form of salt. Salt and water within the body appear almost inseparable. It is difficult, if not impossible, to retain salt without water or water without salt; about six grams of salt will hold about one liter of water. Since about one-third of the total base is balanced by protein or other colloids, given a low serum protein the amount of edema is determined almost if not quite accurately by the amount of salt administered in the diet. Since the greater part of the three to six grams of sodium in the daily diet is added to food as seasoning in the form of salt, it is a relatively easy matter to control the total base by withholding salt. The two to four grams of *potassium* in the daily diet are naturally present in animal and vegetable tissues consumed as food. The alleged antagonism between sodium and potassium may, in part at least, be ascribed to the characteristic distribution of these elements within the tissues, potassium being predominantly within the cells, whereas sodium predominates in the intercellular fluids. It is possible that the bulk of the potassium which occurs in the serum is that which is in transit to or from the cells. The diuretic action of potassium has long been known and applied in practical therapeutics. The mechanism by which it occurs is not clear. It has been suggested that it acts as a substitution product for sodium; this, however, seems unlikely. Whether potassium in the serum in concentrations encountered in clinical practice may be toxic is a debatable question. Toxic manifestations ascribed to potassium may be due to sodium loss. *Chloride* apparently acts solely as a vehicle for the metals, and edema is not ascribed to the inability of the kidneys to excrete chloride; hence the total chloride of the diet is probably of little practical significance.

The mechanism by which readjustment of the acid-base balance of the extra-cellular fluids of the body occurs may be briefly stated as follows: The body as a whole may be considered as a physio-chemical system in which acid and base are held in equilibrium as neutral salts. The equilibrium is delicately maintained. The alteration of one factor automatically alters all others. The total base concentration is the major, immediate factor which

controls the state of hydration. In other words, base holds water. Finally, procedures which tend to shift the reaction of the tissues and extra-cellular fluids toward the acid side—that is, withholding base or administering acid —result in the excretion of base and with it water. Practically this is quite readily accomplished by a low salt diet and the administration of an acid-liberating substance such as ammonium chloride, ammonium nitrate, calcium chloride, or hydrochloric acid in sufficient quantity, or by prescribing a diet that leaves a definitely acid ash. Some of the processes involved in this seemingly simple reaction are still obscure.

The considerations mentioned should be kept in mind in prescribing a practical diuretic regimen for the individual patient. Of first importance is the selection of a diet which will meet the nutritional requirements of a patient who is chronically ill. Otherwise much harm may be done. The diet must be balanced with respect to carbohydrate, protein and vitamin content; it must be adequate in amount and palatable, and for the purpose must facilitate the mobilization and elimination of fluid. Ideally, foods should be selected which leave a neutral or acid ash and which have a low sodium and high potassium content. This may readily be accomplished by reference to reliable tables showing the ash constituents of foods, such as those published by Sherman.[6] Salt should not be used in the preparation of food, nor should it be used as a condiment; potassium chloride, however, may be added from a shaker as a fairly satisfactory substitute. Theoretically and practically, as reported by Barker,[7] it is possible to eliminate edema in many cases solely by the dietary measures described. The addition of potassium chloride sprinkled on food as condiment or " salt substitute " may materially increase the potassium-sodium ratio and facilitate diuresis. In some patients the simple procedure of withholding sodium chloride in the preparation of food or its use as a condiment, and the administration of an acid-liberating salt such as ammonium nitrate in sufficient quantity to overbalance the sodium intake, may effect diuresis and eliminate edema. The administration of an acid-liberating salt of this nature appears, therefore, to be a matter of convenience where great care in the selection of a diet and its preparation may be difficult. Ammonium nitrate in 25 per cent solution in a simple vehicle is well tolerated and may be given in doses up to nine grams daily without serious inconvenience to the patient. Theoretically the acid radical split off from ammonium nitrate should have a diuretic effect on its own account.

The results obtained may on occasion be greatly enhanced by inducing an acute diuresis by means of mercurial or other diuretic preparations. In recent years *salyrgan,* an organic mercurial preparation containing 36 per cent mercury, has come into general use. One or two cubic centimeters of this solution introduced intravenously or deep into the muscles may be effective. It would appear from the reports of Christian and Bartram [8] and of Hermann, Stone and Schwab [9] that mercury has a general specific effect on the colloids of the body as well as a local effect upon the tubular epi-

thelium of the kidney, depressing tubular reabsorption of the electrolytes and water of the glomerular filtrate. The exact mechanism by which this is accomplished seems obscure.

The principles enumerated have a wide application in clinical medicine; the elimination of edema as seen in cardiac failure and nephritis, the reduction of the heart load, the relief of hypostasis, and the removal of pleural and ascitic fluids may prove of material benefit to many patients suffering from a wide variety of diseases. These means may be readily used in general practice over long periods of time both in ambulatory and bed-fast patients. The dangers incident to this method of management are relatively few; however, one does not contemplate the manipulation of forces which may dislocate or readjust the internal environment without giving the possibilities of doing harm serious thought. Practically no serious harm by such management has been recognized. Acidosis in its milder grades has been produced but is readily recognized and as easily combatted. Dehydration of severe grade should be avoided, but this too may be anticipated and prevented by modifying the regimen, by allowing a small amount of salt to be used in the preparation of food, or by reducing the dose of acid-forming salt if such has been prescribed. Methemoglobinemia may be produced in some by administering ammonium nitrate in the doses usually prescribed but it is readily recognized and as readily relieved, as reported by Barker and O'Hare,[10] Eusterman and Keith,[11] and Tarr.[12] Finally, patients themselves, by closely observing their general condition, especially as to body weight or the re-appearance of ankle edema, may soon learn to adjust their own diuretic regimen satisfactorily.

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PROBLEMS OF PULMONARY TUBERCULOSIS IN GENERAL PRACTICE*

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For several years I have been physician to the students at the Harvard Medical School. This experience has led inevitably to a deep interest in the clinical manifestations of pulmonary tuberculosis. I have been dismayed at the seriousness of this disease as it is found in a general practice of this sort. I have been struck by its varied appearance and, above all, I have been impressed by the great responsibility resting upon the family doctor in regard to it. Upon him much depends regarding the early diagnosis of tuberculosis, and his advice on the problems arising in the regulation of such patients' lives is often of paramount importance.

The tuberculosis problem has reached a queer impasse. This disease should be of widespread significance to all doctors, for in 1931, 80,562 new patients were admitted to the 509 special tuberculosis hospitals in the United States. And yet the Commission on Medical Education, in studying the diagnoses reported by a group of general practitioners, finds that the diagnosis of tuberculosis is an uncommon one. The reason for this discrepancy between the frequency of tuberculosis in the community and the rarity of its recognition by the general practitioner is not difficult to explain. Anti-tuberculosis propaganda and the development of specialists in tuberculosis have produced an apathy on the part of many doctors toward this disease. The family doctor thinks that he no longer sees the cases as he used to: only at infrequent intervals do they pass through his hands, for now they are apt to be recognized and segregated by school physicians, industrial physicians, life insurance examiners, or by some special agency designed to combat the spread of the disease. Most cases, too, are treated while the disease is active by specialists in special hospitals. The result is that the general practitioner has lost interest in this subject. He has grown careless in the art of history-taking and physical diagnosis, and has washed his hands of the treatment of tuberculosis. This is an unfortunate state of affairs, for the general practitioner, in spite of the trend of the times, should be as keenly alive to the clinical problems of tuberculosis as ever. If he is a good doctor, his patients and their families will always eventually return to him for advice, no matter through what special hands they may pass on the way, and he remains their court of last appeal. If he is to give sound advice in regard to tuberculosis he must be familiar with it.

There are four clinical types of pulmonary tuberculosis in young people which have aroused my particular interest. These are familiar to every one and easily recognized. The individual cases which I shall present, however, will serve to illustrate some of the reasons why the problems of

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pulmonary tuberculosis continue to be of vital importance to the family doctor.

A young woman, 20 years old, came to the Peter Bent Brigham Hospital in October 1923. Early in the previous spring she had felt unusually tired and lacked her customary buoyancy. Gradually she began to lose a little weight, and presently it was observed that she had a slight afternoon temperature. She went to see two doctors before she came to the Hospital. One said that she was nervous, the other that he could find nothing wrong beyond a rapidly beating heart.

On physical examination there was dullness with tubular breathing and râles at the right apex. Although she said that she had no chronic cough, yet on persuasion it was possible for her to raise sputum containing tubercle bacilli. The roentgen-ray revealed an area of infiltration involving the right upper lobe in the midst of which was a small circular area of decreased density suggesting cavitation.

This case represents chronic tuberculosis beginning insidiously and becoming well advanced before it is recognized. It is a clearly defined typical picture. To me, however, the most important features of this particular case are its subsequent course, and the fact that a good family doctor could have been so helpful. The patient was sent to a sanitarium where the authorities said that after six months she would be well. At the end of this time, however, she was transferred to another sanitarium for another six months. Here she met a young man whom she married.

She appeared to get along splendidly; she was discharged from the sanitarium well, and four years later had a baby. But nine years after her first appearance in our Clinic, when the baby was five years old he developed tuberculosis and his mother began again to have a slight afternoon temperature. An alert family physician might well have been the one to advise her in regard to such matters as marriage and pregnancy, to follow up her case, to keep her under supervision and to outline the proper plan of life for her. As it was, the tuberculosis specialist gave her admirable hospital care, yet after she left the sanitarium, neither he nor any one else was concerned with her method of living, and the end-result was a preventable medical calamity. There are too many cases of this description which keep cropping up year after year in all our hospitals.

A nurse, 25 years old, entered the Hospital in December 1922, with a left-sided pleural effusion. The chest was tapped, and the fluid inoculated into a guinea pig with negative results. Because of the probability that the pleurisy was tuberculous, she was kept at rest for six weeks. At the end of that period, her physical signs were negative, a roentgenogram of her chest showed no positive findings, and gradually she was allowed to resume her work.

About six months later she reëntered the Hospital with a second attack of pleurisy with effusion, the right chest now being involved. This chest was tapped, the fluid inoculated into a guinea pig, and on this occasion the diagnosis of tuberculosis was established. The patient was sent to a sanitarium where she remained for five months. At the end of this time roentgenograms and physical examination were entirely negative as was the tuberculosis fixation test. She was regarded as having merely "suspected tuberculosis."

After leaving the sanitarium she worked for a little over a year. Then she

began to feel too easily tired, to lose a little weight and to be conscious of a rapidly beating heart. There was dullness at both apices with a few persistent crackling râles. Roentgenograms revealed a small but definite area of infiltration in the left apex. She rested for several months and then having gained weight and strength, went to Florida where she obtained an easy job.

This patient felt well until 1928—six years after her original illness. Then, once more, she began to tire easily, to feel conscious of her heart, and to lose weight. There were râles at both apices. Roentgen-ray films revealed fairly extensive bilateral infiltration in both upper lobes. Since then she has gone down hill gradually, has developed cavitation in a slowly spreading process and for more than a year has been bed-ridden.

This case, followed over a ten-year period, illustrates two points: the importance of pleurisy with effusion and the relentless advance of pulmonary tuberculosis in certain individuals.

Pleurisy with effusion is seen not uncommonly in general practice. It should be regarded, always, as being due to tuberculosis. In the Peter Bent Brigham Hospital for many years Professor Christian has advocated immediate withdrawal of the fluid from the affected chest. The procedure is a simple one. The fluid does not tend to recur, and its removal not only makes the patient's breathing considerably easier but also shortens the febrile response to the disease. The immediate treatment of pleurisy with effusion, therefore, is simple.

The follow-up treatment of pleurisy with effusion is more complicated. Patients with this disease should be kept at rest for long periods of time, should have periodic reëxaminations, and should be taught to take care of themselves with the same meticulous regard for detail as with an open lesion. One can never tell when the original focus may flare up into an actively spreading process. The prevention of such an accident lies in the hands of the family physician.

Of the relentless advance of tuberculosis there is little to say except that it occurs under the best of conditions. In this connection, however, I have been struck by the number of people with tuberculosis who have come to the Peter Bent Brigham Hospital, and who have been transferred later to tuberculosis hospitals in various parts of the country, whose relations have kept returning to our house officers or staff for subsequent advice involving such questions as the following: Should the sanitarium doctor be allowed to inject air into the patient's chest or to do a more radical operation? Is hemoptysis an ominous sign? How long shall the patient stay in bed, and is the sanitarium doctor right in allowing the patient to get up so soon? Is it proper for the sanitarium doctor to have the patients' tonsils removed? Does the sanitarium doctor know what he is doing? Questions of this sort, propounded by patients' relatives, have made me feel that the family doctor should occupy a very important strategic position in the management of tuberculosis, between the patient on the one hand and the sanitarium on the other. He can be a very helpful *liaison* officer. The tuberculosis specialist takes care of the patient during an acute phase of a chronic disease

whereas the family physician should take care of the patient during his entire lifetime. Therefore, unless the general practitioner knows what is going on in the progress of medical knowledge of tuberculosis so that he has an intelligent opinion in regard to new therapeutic methods, unless he can take care of his tuberculous patients after they are discharged from various special hospitals and can observe their lesions intelligently, he is not practicing good medicine and is missing an important chance for doing constructive medical work. It is fully as interesting and important for a doctor to make sure that a quiescent tuberculosis remains inactive as it is for him to become trained in such procedures as the technic of artificial pneumothorax.

A 30 year old man entered the Hospital in September 1926. As a boy he had suffered from occasional attacks of dry pleurisy, but these had not been at all disabling. He had a good war record and was not ill during his experience in France. He had spent the year previous to coming to the Hospital in London, where he had been studying, and when he set sail for America in late August he felt as well as possible. On the ocean he seemed a little out of sorts, but attributed this to mild sea-sickness. Shortly after landing he had a sudden attack of pain in the right lower chest, aggravated by deep breathing and accompanied by a low fever, a pleural rub, and later by physical signs of slight hydrothorax. He did not improve; the fever persisted; roentgenograms of the chest revealed a fine diffuse mottling through both lung fields; he began finally to raise sputum and to pass urine and feces which contained tubercle bacilli, and at last he developed the clinical picture of a terminal meningitis. He died about three months after he first began to feel unwell. The necropsy revealed a generalized miliary tuberculosis with involvement of almost every organ.

Miliary tuberculosis occurs in general practice rarely, so that it is often forgotten and therefore not suspected; under any circumstances it well may afford a baffling diagnostic problem. The description of miliary tuberculosis which appeared in the first edition of Osler's Practice forty years ago has not been improved on by anything written in our more modern textbooks. Osler reminds us that there are chiefly three clinical forms of generalized tuberculosis: the typhoid form with the symptoms of an acute general infection; cases in which pulmonary symptoms predominate; and cases in which the cerebral or cerebrospinal symptoms are marked. In the typhoid form—which seems to me to be the one most difficult to recognize—the patient presents the symptoms of a profound infection which simulates and is frequently mistaken for typhoid fever. Osler points out a differential point well worth remembering: namely, that the greater frequency of the respirations and the tendency to slight cyanosis are much more common in tuberculosis. He reminds us that in general tuberculosis the spleen may be enlarged—but not as early or as markedly as in typhoid—and that reddish spots on the skin may develop which can be confused with rose spots. There is no special treatment and the prognosis usually is hopeless. However it is worth remembering that occasional cases recover. A few years ago Professor Christian had a negress [1] in his wards at the Peter Bent Brigham Hospital with miliary tuberculosis as demonstrated by find-

ing the histologic picture of tuberculosis in one of the skin lesions which developed, as well as by typical roentgen-ray films of her chest. She ran a protracted febrile course for many months but eventually got well and still shows herself in our Out-Door Department from time to time to prove the tale.

In my experience with our medical students, tuberculosis, I am glad to say, has appeared very infrequently. When it has appeared, it has shown up unexpectedly, in boys previously supposed to be perfectly healthy, and with symptoms simulating an acute upper respiratory infection, or as a sudden hemoptysis.

In 1927, a robust-looking young man went away on a vacation. He was in good condition so far as he knew. He played a violent game of tennis one morning and immediately after it, began to raise large quantities of bloody sputum. When he was admitted to the Hospital he looked critically ill. Over the right upper lobe were râles, and exaggerated voice and breath sounds. Roentgenograms of the chest showed marked infiltration through both lungs suggesting an acute bronchopneumonia. The sputum contained tubercle bacilli.

He was put to bed. The temperature quickly fell and within two weeks was entirely normal. The cough disappeared, the râles and signs of consolidation cleared up rapidly and no more sputum was forthcoming. He was able to return to work within a year following the hemoptysis and has been well and active ever since.

Cases of this type are encountered from time to time, and are always at first seen by the family doctor. At the onset they look as though their outlook might be hopeless and yet they may run a very benign course. The roentgen-ray picture often appears to show a much more extensive lesion than actually is present, due, apparently, to hemorrhage infiltrating the lung. In fact, not infrequently, the patient whose tuberculosis becomes manifest by a pulmonary hemorrhage is the lucky one, for the diagnosis is established immediately and proper treatment is instituted without waste of time.

These instances, perhaps, are sufficient to illustrate the growth of my feeling in regard to the tuberculosis problem. Other individual cases keep coming to mind—a case for instance of old, supposedly healed tuberculosis which became fatally activated by a surgeon's injudicious use of ether without the family doctor's consent; a case of quiescent tuberculosis brought to life by the uncontrolled use of the Alpine lamp when it was the latest fashion; a case of tuberculous empyema recognized and saved from improper surgical treatment. In brief, as I have seen pulmonary tuberculosis, not as a specialist, but as an individual engaged in more general medical work, I have acquired gradually certain very definite convictions in regard to it. Pulmonary tuberculosis is still so common a disease as to be ever-present, and general practitioners are seeing it frequently, perhaps failing to recognize its significance. All must learn to make the diagnosis at the earliest possible moment, and must take an increasing responsibility in learning how to treat it to best advantage. The treatment of tuberculosis while it is acute, will probably and properly continue in the hands of well trained

specialists. After the acute stage is over, when the disease has become quiescent, the majority of cases will return to the hands of their family doctors. The family doctor, therefore, must take an increasingly active part in the campaign against tuberculosis in order to prevent the occurrence of such common catastrophes as I have outlined.

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A GRAPHIC STUDY OF THE CHANGES IN THE MUSCULAR ACTIVITY OF THE STOMACH ASSOCIATED WITH CERTAIN EPIGASTRIC SYMPTOMS*

By P. B. Welch, M.D., F.A.C.P., *Coral Gables, Florida*

Some years ago (1924) while the effect of feeding upon the muscular activity of the colon was being studied,[1] it seemed that a similar investigation of the muscular activity of the stomach might satisfactorily explain the almost constantly presented symptom of epigastric distress, the distress usually described by the patient as "gas." A perhaps cursory survey of the literature failed to supply any satisfactory physiopathologic explanation of the association of this symptom complex with so many different kinds and gradations of abdominal pathologic lesions or disturbed functions.

It seemed opportune to make a beginning at least by recording exactly what changes in muscular activity were occurring in the stomach during these so called "gas" attacks. Accordingly, such an investigation was undertaken.

Kymographic tracings were made of the muscular activity of the stomach both in health and in the presence of varying abdominal symptoms and lesions. The tracings were obtained by placing a condom balloon of known capacity into the fasting stomach. The balloon was connected by means of a Rehfuss tube to a pear flask which was partially filled with water, leaving an air space above the fluid level. This air was in turn connected to a Brodie recording bellows[2] which recorded upon a slow speed kymograph.

These experiments were invariably begun upon a fasting stomach (14 to 18 hours) with the patient in a comfortable reclining position. The height of the pear flask containing water and air was adjusted to develop only sufficient hydrostatic pressure to gently distend the balloon in the stomach.

After insertion of the balloon it was left in place long enough for the patient to become accustomed to the presence of the small Rehfuss tube and for the stomach to become accommodated to the presence of the balloon. The movements of the fasting stomach were then recorded. When the typical hunger contractions, described by Carlson[3] and others, were present the patient while still reclining was hand fed. The feeding consisted of cereal and milk, or milk and graham crackers. The patient remained relaxed and did not lift the head during the feeding. This precaution was necessary to avoid any increase in intra-abdominal pressure.

Tracings were continued for a period of three to seven hours, usually lasting two hours after the feeding. By prolonging the tracings after feeding it was possible to have a record of the digestive cycle of the stomach. The abnormalities of gastric motility naturally developed consecutively dur-

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ing this period, duplicating the condition producing the symptoms in each case.

A series of 16 tracings was made on humans who had clinical evidence of some abdominal disturbance. Tracings were made on normal humans and on dogs (figure 1) with permanent gastric fistulae. These latter were

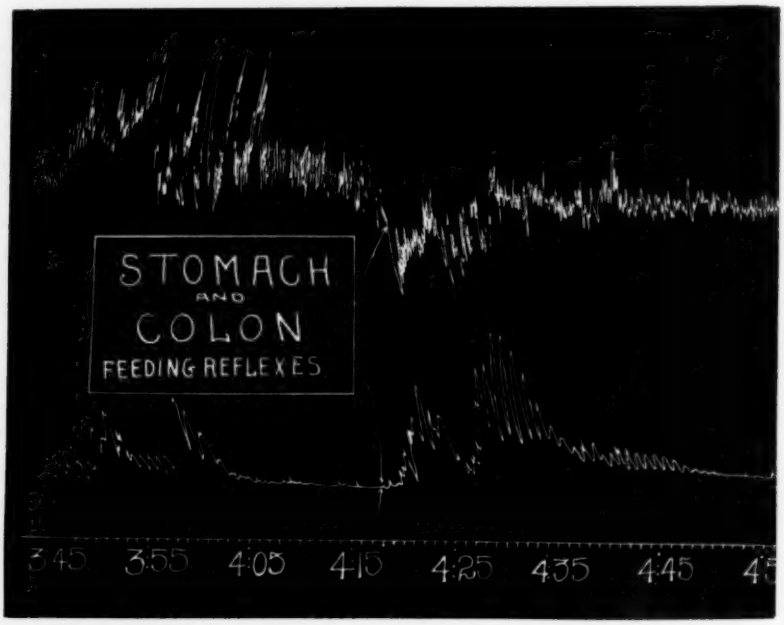

FIG. 1. Simultaneous tracings from stomach and colon of dog with permanent gastric and colon fistulae, showing normal inhibition and relaxation of the muscular activity of the stomach at the time of feeding. Lower tracing shows normal increase in muscular activity of colon in response to feeding.

made as controls and completely corroborated the work of Carlson[4] and others who found that normally hunger contractions of the stomach are inhibited and gastric muscular tone is lowered upon the taking of almost any kind of foodstuff into the mouth. Indeed even indifferent substances such as paraffin were shown to produce a similar though fleeting effect. This reflex is doubtless an appetite or taste reflex similar in its production to that seen in the colon.[1]

In 14 of this series of 16 cases the normal immediate inhibition was not only absent but reversed. Usually upon the first taste of food there was an immediate and sometimes amazing increase in muscular tone of the stomach. Some of these marked inversions actually emptied the balloon almost completely indicating a virtual obliteration of the gastric lumen. Usually there was an associated inhibition of peristalsis but not invariably so. Figure 2 shows a well marked inversion of the taste reflex.

There did seem to be some quantitative relationship between the intensity of the symptoms and the degree of inversion as shown by comparison

of figures 2 and 3, the latter showing a moderate inversion with moderate symptoms associated with an irritable colon, as compared to figure 2 with rather intense symptoms and a marked inversion associated with a chronic appendicitis.

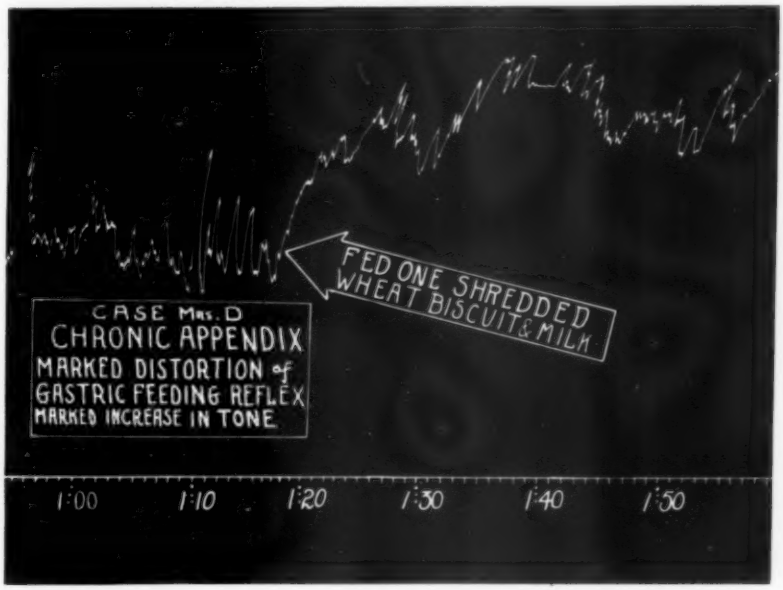

FIG. 2. Tracing from human stomach (Case No. 1) showing marked inversion of the feeding or taste reflex associated with chronic appendix with strong sensory stimuli.

Table 1 correlates the diagnosis, character and intensity of symptoms and degree of inversion of the reflex. In every instance where the sensory stimulation was strong there was a very marked disturbance of muscular activity. In four instances the sensory stimulation was apparently stronger than the inversion, probably due to the patient's susceptibility to sensory stimuli.

In table 2 are grouped those 10 cases in which fractional gastric analysis was done.

In five instances there was a complete achlorhydria. Two of these showed a normal gastric taste reflex. In both these instances the tracings were made because of the absence of hydrochloric acid. In one case the patient was symptom free. The other had been under treatment for a month for gastric atony and achlorhydria. In this group of five cases the absence of free hydrochloric acid apparently had no influence upon the muscular activity of the stomach. The same may be said of those classified as hypochlorhydria and hyperchlorhydria.

It has long been known that chronic appendicitis, gall-bladder disease and other abdominal visceral diseases produce reflex spasm of the pylorus. Carlson and Litt[5] pointed out that "mŏtor disturbances of the pylorus may

TABLE I

Correlation of the Diagnosis, Intensity of Symptoms and Degree of Inversion of the Reflex

Case		Diagnosis	Abdominal symptoms	Symptom intensity	Degree of inversion
Mrs. D.	1	Chronic appendicitis.	Post prandial epigastric distress: also right upper quadrant distress.	4+	4+
D.K.	2	Chronic appendicitis.	Post prandial epigastric burning: eructations.	2+	3+
C.E.A.	3	Chronic appendicitis; duodenal ulcer.	Post prandial epigastric pressure: eructations: abdominal soreness.	3+	4+
R.P.	4	Chronic appendicitis; duodenal ulcer.	Post prandial epigastric distress: right lower quadrant soreness.	3+	3+
E.H.B.	5	Duodenal ulcer.	Epigastric soreness: eructations.	3+	4+
G.W.K.	6	Chronic duodenal ulcer; moderate stenosis.	Soreness l.u.q. eructation: occasional vomiting.	3+	4+
M.J.C.	7	Simple gastric ulcer; pruritus ani; achlorhydria.	Epigastric fullness and soreness—eructations.	1+	3+
N.H.B.	8	Colon stasis; irritable colon; over-eating.	Epigastric pressure, eructations.	2+	2+
G.P.	9	Hypertrophic hepatitis.	General epigastric pain—eructations.	4+	4+
McL.	10	Glossitis subacute: hemorrhoids; irritable colon.	Epigastric burning.	3+	2+
G.H.	11	Gastric neurosis; colon stasis; achlorhydria.	Epigastric burning, pressure and eructations.	3+	2+
Mrs. R.	12	Pernicious anemia; irritable colon; achlorhydria.	Epigastric gnawing pain.	3+	1+
F.S.	13	Marked colon stasis; irritable colon.	Epigastric gnawing pain.	1+	1+
C.B.B.	14	Hemorrhoids; irritable colon; marked stasis.	Epigastric fullness and pressure.	2+	1+
D.W.E.	15	Achlorhydria; gastric atony.	Symptom free.	-	None
J.H.	16	Achlorhydria.	Symptom free.	-	None

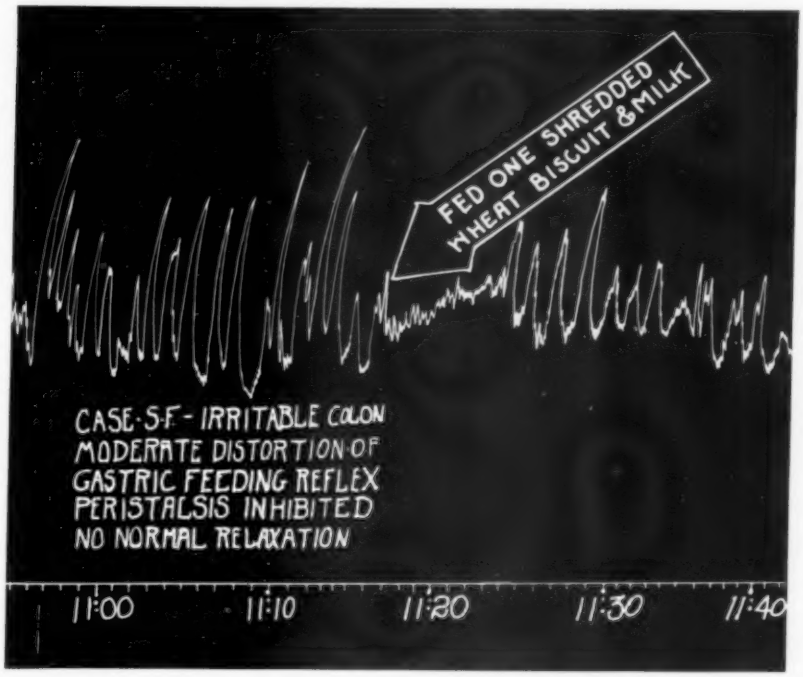

FIG. 3. Tracing from human stomach (Case No. 13) showing moderate inversion of the feeding or taste reflex associated with an irritable colon with moderate sensory stimuli.

be induced '.....' by excessive irritation of most, if not all, sensory nerves, particularly those of the abdominal viscera."

The work done in this series would seem to indicate that excessive stimulation of the sensory nerves, of the abdominal viscera at least, causes reflex motor disturbances not only of the pylorus but also of the rest of the gastric musculature.

The chief purpose of this presentation has been to show that a relationship exists between the symptom complex commonly complained of as "gas" and certain departures from the normal muscular activity of the stomach consisting of a reversal of the normal taste reflex.

While the number of experiments in this series is perhaps too limited to permit of any generalizations, it does seem justifiable to draw certain tentative conclusions which may prove helpful in the interpretation of certain symptoms which daily are presented to the gastroenterologist and to the general practitioner.

CONCLUSIONS

1. There exists a definite etiologic relationship between the symptoms of epigastric distress, fullness and pressure, and muscular spasm of the stomach upon the placing of food in the mouth.

2. This spasm is a reversal or inversion of the normal appetite or taste reflex and consists of an increase in gastric muscular tone instead of relaxation and inhibition.

TABLE II

Showing Gastric Analysis in Ten Cases and Degree of Inversion of the Feeding or Taste Reflex, There Apparently Being No Relationship between the Degrees of Acidity and the Inversion of the Reflex.

		Degree of acidity					Degree of inversion
		Fasting	30 min.	60 min.	90 min.	120 min.	
Case 11	Free acid	0	0	0	0	0	None
	Total acid	50	44	36	32	28	
Case 12	F	0	0	0	—	—	2+
	T	28	44	50			
Case 13	F	0	0	0	0	0	1+
	T	—	20	20	28	40	
Case 14	F	0	0	0	0	0	None
	T	—	30	54	56	54	
Case 7	F	0	0	0	0	0	3+
	T	—	—	—	—	—	
Case 2	F	0	0	0	10	26	3+
	T	44	70	68	92	90	
Case 6	F	0	0	0	0	38	4+
	T	26	30	30	26	90	
Case 4	F	50	36	44	60	56	2+
	T	80	66	94	120	92	
Case 3	F	80	12	0	0	0	4+
	T	138	36	30	38	42	
Case 5	F	102	56	50	86	76	4+
	T	136	106	88	118	118	

3. There is an apparent quantitative relationship between the intensity of sensory stimulation and the degree of inversion of the appetite reflex.

4. These sensory stimuli may be intra- or extra-gastric in origin.

5. The inversion of the appetite reflex is apparently independent of the secretion of hydrochloric acid, being apparently purely a motor phenomenon.

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THE RELATIONSHIP OF THE AUTONOMIC NERVOUS SYSTEM TO GENERAL MEDICINE*

By Thomas P. Sprunt, M.D., F.A.C.P., *Baltimore, Md.*

Professor Cannon has clearly and concisely outlined the marvelous biological mechanisms by which the fluid matrix of the body is preserved in healthful equilibrium and by which its remarkable reserve forces are mobilized and made available for extraordinary activities. The autonomic nervous system is among the most important mechanisms in the preservation of this homeostasis that Cannon has poetically dubbed the wisdom of the body. One might, then, readily expect that this system would play an equally important rôle in the manifestations of the folly or of the unhappiness of the body that constitutes disease.

As in the preservation of homeostasis in health it is often impossible to differentiate sharply between the effects of nerve impulses and of humoral activities, so under pathological conditions we not infrequently must consider a maze of inseparable effects produced by nerve impulses, by hormones, and by other chemical agents. It is well to keep this fact constantly in mind in any consideration of the part played by the autonomic nerves in disease processes.

The autonomic or the vegetative nervous system is divided anatomically and physiologically into two definite systems, namely the sympathetic division or thoraco-lumbar outflow and the parasympathetic or cranio-sacral outflow. Of these, the parasympathetic system seems designed especially for individual organ effects and subserves a group of reflexes chiefly protective, conservative, and upbuilding in their service. The sympathetic division on the other hand is well adapted to the exercise of general and widespread activities and has much to do with the preservation of homeostasis or the prevention of serious changes of the internal environment both during ordinary activities and under conditions of stress. Where these two systems send fibers to the same organ as they do in the case of most of the viscera, their activities are usually antagonistic to each other, the one exciting and the other inhibiting the secretion or the motility of the viscus, hence when the nervous relationships to an organ are known one can generally recognize a symptom on the part of the structure as of sympathetic or of parasympathetic origin.

Autonomic Nervous Reflexes in Organic Disease

It is as a mechanism for the development of symptoms and signs in organic disease that I would first stress the activities of the autonomic

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nerves. Autonomic symptoms may arise by reflex action from a stimulus in any part of the body or by the effects of humoral agents upon centers in the central nervous system. They may be inaugurated by a great variety of stimuli. An important factor in many or in all cases is the constitution of the patient, for in one person a given stimulus may be adequate to produce a symptomatic effect whereas in another person the same stimulus may be without such effect. Some years ago the Viennese clinicians, Eppinger and Hess, announced their conviction that certain people were constitutionally predisposed to parasympathetic symptoms while others were prone to the development of symptoms due to sympathetic activities. Of the pharmacodynamic agents that were developed for testing such potentialities, adrenalin was used to test the sensibility of the sympathetic nervous system while pilocarpin was used as a stimulant for the parasympathetic system, and atropin as an inhibitor of its action. Most of the more recent workers in this field are agreed that sharp differentiation between sympathicotonic and vagotonic states and constitutions are not practicable nor in accord with the available data. Nevertheless, this conception has been a great stimulus in the study of the symptomatology of disease.

The reflexes by which symptoms arise are of different complexity, varying from the simplest axone reflex, through the ordinary spinal reflex, to much more complicated pathways including a number of intercalated neurones on the afferent side, a participation of several centers in the central nervous system, and an outflow through different efferent channels. A gastric ulcer may serve as a stimulus in a relatively simple reflex producing hypersecretion and hypermotility of the stomach. An inflamed appendix or gall-bladder may reflexly produce the same phenomena in the stomach. How frequently the patient with early pulmonary tuberculosis complains of a prolonged cold in the head or of gastrointestinal symptoms. Viscero-motor reflexes may originate from a stimulus within a viscus and affect the skeletal musculature overlying that organ. In the case of the so-called viscero-sensory reflexes the stimulus again arises within the viscus and its effect is the referred pain to the body wall that may be so helpful as a diagnostic sign. As there are many reflex arcs from organ to skin (viscero-cutaneous reflexes) so there are reflexes from skin to organs (cutaneo-visceral reflexes), the latter forming the basis for much that is most useful in our methods of physical therapy. Such manifestations of pathological physiology in the autonomic nervous system are of daily use to us in diagnosis, in prognosis and in therapy.

In certain types of diseases, as for example, in exophthalmic goiter and other endocrinopathies, and in the manifestations of allergic phenomena, autonomic disturbances are particularly prominent. Again, they predominate in certain paroxysmal syndromes like epilepsy, migraine and the vascular crises that occur in different regions of the body. In his analysis of important symptoms of early tuberculosis, Pottenger lists, as due to autonomic reflexes, hoarseness, tickling in the larynx, cough, digestive dis-

turbance (hypermotility and hypersecretion), circulatory disturbance, chest and shoulder pains, flushing of the face, spasm of muscles of the shoulder girdle and diminished motion of the affected side. Similarly, in the analysis of symptoms of any important organic illness, one may find evidence of many reflex disorders and realize how richly the visceral nerves contribute to the symptomatology of structural disease.

The Autonomic Nervous System and Fever

There exists in fever an interesting example of the interrelationship of the autonomic nervous system with a fundamental symptom of a large group of diseases, and the current interest in this relationship justifies some detail in its consideration. There is reason to believe, of course, that fever is one of the protective mechanisms of the body, that it may inhibit the growth of certain thermolabile organisms, that it may heighten the production of immune antibodies, and that it may be of protective service in other ways.

That the autonomic nervous system plays a rôle in heat regulation and also in the production of fever is indicated by abundant data. It has been amply demonstrated by pathologists and by neurological surgeons that tumors and other lesions in the diencephalon and in the walls of the third ventricle, as well as operative traumata in these regions, are sometimes attended by marked hyperpyrexia. On the other hand, heat regulation is decidedly disturbed and fever cannot be experimentally produced in animals whose sympathetic nervous systems have been removed or whose cervical cords have been severed. Cannon's sympathectomized cats could not maintain a normal temperature in a cold room and his sympathectomized monkey suffered a sun-stroke when placed out of doors on an ordinary summer day. From a clinical standpoint Gordon Holmes has reported among his patients with acute war injuries to the spinal cord a series of 10 cases with extensive lesions at the cervical enlargement that showed a remarkable clinical picture characterized by subnormal temperature, slow pulse, low blood pressure, a scanty secretion of urine, and a stuporous or extremely lethargic mental state. The body temperature was as low as 80° F.

Although the participation of the autonomic nervous system is recognized we have but little satisfactory understanding of the manner in which fever is produced. It seems altogether probable that the difficulty lies not so much in an overproduction of heat as in a disturbance of its elimination. Although the very marked increase in the heat production of exercise is compensated by an equivalent heat loss so that no sustained rise of body temperature occurs, the relatively small increase in heat production in fever is not so accurately compensated. Clinically we may watch the mechanism at work in the acute onset of fever with a chill. There is marked peripheral vasoconstriction; the skin is dry and cold; gooseflesh appears. The patient feels cold, shivers and shakes, covers himself with blankets and although his sensation of cold continues the body temperature is at its highest during

the chill. Other reflex mechanisms may play a part in the increased body temperature.

In his study of the skin temperatures of children Talbot was impressed with the importance of the skin of the arms and legs in the conservation or dissipation of body heat. He found that during fever the reaction of the skin to surrounding temperatures, changes definitely when the temperature of the body reaches approximately 39° C. At this point some fundamental change takes place in the physiology of heat excretion.

When we consider conversely the influence of fever upon the autonomic nerves it is of course often difficult to differentiate between the effect of the fever itself and that of the toxins that produce it. The induction of fever by physical methods has shown that many of these effects are due to the elevation of temperature per se. As Talbot has indicated, at a certain level of temperature a change occurs in the skin of the extremities and in the dilatation of the cutaneous vessels. This is in apparent harmony with a general change of tone in the vegetative nervous system in fevers. Beaumont, in 1833, recorded a decrease in the gastric secretion in febrile states, a fact that has been confirmed by many clinical observers. The fact has also been demonstrated in Pavlov pouch dogs that increased body temperature itself, apart from any possible action of bacterial toxins, depresses the gastric glands. It is a matter of clinical observation that conditions like asthma, paroxysmal tachycardia, and gastric crises that are totally or in part produced by mediation of the vegetative nervous system may be greatly ameliorated when the patient has a febrile illness. Danielopolu has recently called attention to this fact and to what he considers the similarity in the effect of fever and of anesthetics upon paroxysmal syndromes. He believes that both with fevers and with anesthesia there is a modification of the autonomic tone and he affirms that if we follow daily the state of the vegetative system after anesthesia we see that the vegetative tone is not restored for the most part very rapidly but that there is necessary a certain time, several days to several weeks, before the normal tone is fully recovered. He believes that it is common during febrile attacks for such paroxysmal syndromes as those mentioned above to disappear temporarily, to return at a variable period after the fever is gone. He studied the state of the vegetative nervous system during an epidemic of typhus fever and found that doses of adrenalin that ordinarily produced an effect must be increased very markedly during the fever in order to encompass a similar effect. The more severe the fever and the toxemia, the more slowly does this test return to normal after the febrile period.

The influence of fever and of anesthesia on the autonomic nerves is well exemplified in the case of the vasoconstrictors of the extremities, and this fact has been put to definite and practical use in the differential diagnosis and in the therapy of peripheral arterial diseases. A study of the vasoconstrictor gradient or of the vasomotor index is now an essential step in the determination of the type of therapy to be used even in the predominantly occlusive conditions.

The recently devised methods for the induction of fever by electricity offer a new opportunity for the study of its possible effects upon autonomic nervous mechanisms.

The Diencephalic Centers and Metabolism

Earlier students of the autonomic nervous system thought of centers for its reflexes only in the spinal cord. Later, centers in the medulla were recognized and still more recently the diencephalon has been subjected to intensive study. The diencephalon is that small portion of the interbrain laid down early in philogenetic history and situated between the hypophyseal stalk and the floor of the third ventricle. Beattie, Cushing, Biedl and their collaborators have been particularly active in studying the interrelationship of the diencephalic centers with the posterior lobe of the hypophysis on the one hand, and with the thalamus and the cerebral cortex on the other hand. The confirmation and acceptance of these studies will afford a welcome correlation of conflicting opinions concerning the relative importance of the posterior lobe of the hypophysis and of the adjacent nerve tissues on water metabolism (diabetes insipidus), fat metabolism (cerebral adiposity or emaciation), disturbances in heat regulation, in basal metabolism, and in other phases of metabolic activity.

In this hypothalamic region three cellular areas in general are described, an anterior or supraoptic nucleus, the median or tuberal collections in the tuber cinereum, and the posterior or supramammillary center. From these areas, and particularly from the first two, there are described nerve fibers passing downward, becoming concentrated in the stalk of the pituitary and distributed throughout the posterior lobe to its epithelial investment. There are two views concerning the mechanism by which the posterior lobe and pars intermedia may affect these hypothalamic centers; first, the possible passage of the secretion through the tissues of the posterior lobe and infundibulum into the third ventricle, and second, a vascular mechanism described by Popa and Fielding as a "portal" circulation through which the venous blood from the pituitary passes into the tuber cinereum and bathes the tuberal nuclei. Cushing and Beattie believe, partly on an anatomical basis, and from the results of electrical stimulation, partly on the basis of pharmacodynamic studies by the injection of pituitrin and of pilocarpin into the cerebral ventricles, that the supraoptic nucleus and the tuberal nuclei subserve parasympathetic impulses and that the posterior diencephalic center is connected with the sympathetic outflow. Upon the integrity of the posterior nucleus depends the "sham rage" (a typical sympathetic storm) in decorticated animals described by Cannon and by Bard. The further possibility has been suggested that the posterior lobe of the hypophysis may bear the same general relationship to the parasympathetic nervous system that the medulla of the adrenal gland bears to the sympathetic division.

Josefson has reported the case of a man, aged 32 years, who presented

the following clinical features: emaciation, anorexia, weakness, mild somnolence, a brief phase of polyuria and polydipsia, dryness of mouth and throat, feelings of cold, falling out of hair of scalp and loss of body hair, changes in nails and teeth, loss of libido and potentia, dizziness, depression, occasional headaches, achylia gastrica, retarded basal metabolic rate (minus 23 per cent), arterial hypotension (85/60), and hypoglycemia. At the autopsy a small tumor of hazel nut size was found in the diencephalon in the region of the mammillary bodies. The viscera were of small size and the endocrine glands especially were atrophic, including the hypophysis which, however, was normal on histological examination. The ribs were thin and fragile.

We have recently studied a similar case but without the opportunity of an anatomical examination.

It is of great interest that so many symptoms and signs usually attributed to primary endocrine dyscrasias seem in this case to be due to a small lesion in that part of the brain, the site of the most important centers of autonomic nerve impulses. One may conjecture concerning a possible secondary rôle played by the hormones.

Psychic Influence upon the Autonomic Nervous System

The close anatomical relationship of these centers in the diencephalon with the thalamus, where resides the central mechanism for the integration of the emotions, and with the cerebral cortex, the seat of the higher intellectual powers, suggests at once an anatomical basis for the well known effect of psychic processes upon the autonomic nervous system and through it upon the normal and the pathological physiology of the viscera. Cushing says in regard to the diencephalon: " Here in this well concealed spot, almost to be covered by a thumb nail, lies the very mainspring of primitive existence, vegetative, emotional, reproductive, on which, with more or less success, man chiefly has come to superimpose a cortex of inhibitions." In this region too are hidden some of the mysteries of the rhythm of the body, including the mystery of sleep, the changes in the autonomic nervous system that occur in sleep and the similar changes in hypnotic states.

The physiologists, Pavlov, Cannon, Carlson, and others, have abundantly shown the influence of psychic processes upon the vegetative system under normal and under abnormal conditions. When one understands the readiness with which lower animals may be conditioned to unusual autonomic reflexes he can the more easily appreciate the large part that conditioned reflexes must play in the life of man, in his usual behavior as well as in his neurotic reactions. Often the conditioning stimulus may have been more or less obscured by time and by superimposed events. Vegetative phenomena of psychic origin may complicate organic disease and they may play a conspicuous part in the symptomatology of a neurosis.

In the dysharmony of nervous function that is a neurosis, or the expression of a vital conflict, the inherited material or the constitution of the

patient plays a major rôle. Most or all of us doubtless react at some time to our conflicts in a neurotic manner but the majority, by reason of sufficiently stable constitutions, escape a major neurosis. In those persons sufficiently predisposed we see the development of affective disorders, of hysteria, of psychoneurotic states, with any of which there may occur more or less widespread and distressing participation of the autonomic nervous system, with feelings of tension, with headaches, respiratory symptoms, cardiac disturbances, gastrointestinal derangements, peripheral vasoconstrictions, endocrine imbalance, and metabolic changes. Although the emotions cannot be weighed or accurately measured, the autonomic effect of these emotions, as Emerson remarks, on the glucose tolerance of a previously well standardized case of diabetes, can be measured in terms of grams of sugar in the urine, milligrams of glucose in the blood, and of units of insulin necessary to restore the patient to a satisfactory condition. They may also be measured at times by the difficulty we experience in securing basal conditions for an estimation of the metabolic rate.

The autonomic symptoms in the nervous patient are no less real than vegetative nervous reflexes in the patient with organic disease. The mechanism of the symptomatology in the two classes of patients is very much the same. The stimulus is different; the reflex arcs are different; but the effects may differ not at all and may be even more poignant to the sensitive patient with a functional disturbance. In a neurosis we have not a weakening of nervous function but an increased intensity of reflex activity.

In this connection two interesting questions arise. The psychic phenomena, the emotional stimuli, affect the entire body. What determines the choice of an organ for the manifestation of dysharmony in any given case? Why should this patient with an affective disorder complain of constant nausea, of an aversion to food, and of abdominal pain, and another patient with similar emotional reaction be afflicted with headaches and palpitation? The related question of perennial interest is this: Do functional vegetative disturbances lead to structural organic diseases? In answering the latter question I should say that many of us, I am sure, believe that functional autonomic disorders do eventuate in organic disease. We note the apparent effect of the emotions in the development of exophthalmic goiter, of similar influences in the genesis and in the course of arterial hypertension and its sequelae, in angina pectoris and in bronchial asthma. From Cushing's laboratory recently comes a statement of the relationship of cerebral lesions to gastric ulcers in man and the report of experimental production of erosions and ulcers in animals by stimulation of the vagal centers by intraventricular injections of pharmacodynamic materials. But there is another school of thought ably advocated by Ingvar, who believes that functional nervous states do not cause structural organic disease. He points out the insignificant effects of organic nervous diseases upon the viscera with the exception, in a minor way, of encephalitis lethargica that may give rise to dystrophia adiposogenitalis and to diabetes insipidus. He

speaks of hysteria as the great neurosis and is impressed by the rarity of organ changes in this disease. He says that the experiences of the Great War do not support the idea of a purely psychogenic exophthalmic goiter. He believes that many ailments previously classified with the neuroses have been shown by better diagnostic methods to be really organic diseases. He answers both questions by saying that psychic disturbances affect the entire organism, the excitations go over the whole body, and wherever there is a constitutional inferiority of a tissue or a damaged organ with already a predisposition to irritation, symptoms from that organ become manifest. These organ defects are often latent, in his opinion, and he prefers to think that the organic disease is not caused by nervous phenomena but is really uncovered by them. Although he takes this point of view he does not wish in any way to belittle the importance of the emotions in the course of disease. We may not forget that the body and the mind are one. However we may disagree with his main thesis or with any of his premises, we may well accept his statement that a neurosis is a disorder of the personality; not only the organ affected but the person must be treated. And whoever would undertake to treat the neuroses should do so with a background of thorough knowledge of internal medicine and have every facility at his disposal for the utilization of modern diagnostic methods.

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EDITORIALS

DOCTOR WILLIAM BLAIR STEWART

IN THE early records of the American College of Physicians, under date of December 29, 1916, appears a minute showing that Dr. W. Blair Stewart was elected to Fellowship at a meeting of the Council at the Astor Hotel, New York City. This was very shortly after the first steps had been taken towards the formation of the College; and at this same meeting the Constitution and By-Laws were adopted and the first regular Officers of the College elected. In the seventeen years that have since elapsed the name of Dr. Stewart reappears very frequently in the minutes. From the first he had faith in the future of the College and felt that it was destined both to represent and to serve physicians in the field of Internal Medicine. He identified himself with this purpose of the College and from the time of his election to Fellowship he was a regular attendant at its annual meetings. He was elected a member of the first Board of Governors at the Detroit Clinical Sessions on February 25, 1926, to represent the State of New Jersey. In 1930 he was reëlected and unanimously chosen as Chairman of the Board of Governors; and by virtue of that position became ex-officio a member of the Board of Regents. At the expiration of Dr. Stewart's second term, which occurred at the recent Montreal Clinical Session, he was persuaded again to accept election for a term of three years and again was unanimously elected as Chairman of the Board of Governors. Those who were present on that occasion will find pleasure in the memory that Dr. Stewart in his short address of acceptance was visibly moved by the spontaneous testimonies of confidence and esteem which had accompanied his election.

This long career of service to the College has been brought to a close by Dr. Stewart's sudden death. The College has lost one of its most valued officers and innumerable members of the College will feel at future meetings the absence of a friend. His simplicity of manner, his honesty, and his quiet humor drew men to him. Though possessed of sturdy convictions, he was tolerant of the contrary opinions of others. In the chair he maintained the dignity of his office and quietly kept discussion in practical and purposeful channels. Under his wise guidance many problems of the College were brought to a solution. Dr. Stewart's generous interests extended in many directions, both professional and civic. His important accomplishments brought him many honors. His duties as a Governor of the College were nevertheless always fulfilled with the utmost thoroughness and promptness. There was no detail concerning the membership from his state but what received his thoughtful consideration.

The spirit and labors of such men as Dr. William Blair Stewart have made possible the growth of the American College of Physicians. His loss will be sorely felt. His memory will enrich our traditions.

ENCEPHALITIS

PRIOR to the first waves of the great epidemic of lethargic encephalitis the medical literature contained relatively few references to the non-suppurative inflammations of the brain. Our knowledge of encephalitis, as Zappert has rightly said, falls historically into three periods: before the epidemic, during its height, and since. This third period, which is still in progress, should be of lively interest to the clinician.

It seems probable that since the onset towards the end of the war of the first epidemic of lethargic encephalitis (Economo's disease), the frequency not only of this condition but of other forms of encephalitis as well has been far greater than in former years. Not only have outbreaks been observed of primary encephalitis apparently distinct in type from the lethargic form, but the incidence of the so-called secondary or post-infectious encephalitides has been unusually high. The writings of many experienced clinicians[1, 2, 3] are in agreement on this point, even though it is realized that allowances must be made for the popularization of knowledge of the condition with consequent freer diagnostic use, and sometimes abuse, of the term encephalitis.

Lethargic encephalitis, though now infrequent, still persists both in the United States and in European countries, and as recently as 1929 a serious epidemic outbreak occurred in Japan. In spite of great activity in research the etiologic agent which causes this disease is still undiscovered; its pathology, however, the clinical features of its course, and its sequelae are fairly well established. While there are many aberrant forms, the disease is especially characterized clinically by the occurrence of the somnolent-ophthalmoplegic, the hyperkinetic, and the amyostatic or Parkinson-like types. The latter are frequently of a slowly progressive character, and may first appear following a latent period of many months after the acute attack. Other typical sequelae are the myoclonic and bradykinetic disturbances of motility, the oculogyric and respiratory tics and the psychic alterations. Pathologically lethargic encephalitis is preëminently a disease of the gray matter manifesting itself in greatest intensity in the midbrain, particularly in the substantia nigra, in the interbrain and less severely in the gray substance about the fourth ventricle. The perivascular infiltrations and other features which characterize its scattered lesions are similar to those found in the focal lesions of poliomyelitis, rabies and Borna's disease in horses.

In addition to this distinctly marked entity, there have occurred in the last fifteen years numerous other types of primary encephalitis, either as sporadic cases or in the form of localized epidemics. Economo[2] mentions under this heading the occurrence in Australia and in Japan of epidemics of

[1] ZAPPERT, J.: Der jetzige Stand der Enzephalitisfrage im Kindesalter, Wien. klin. Wchnschr., 1932, xlv, 737–744.

[2] VON ECONOMO, C.: Gibt es verschiedene Arten von epidemisch auftretenden Encephalitiden oder gehören sie alle zur Encephalitis lethargica?, Wien. klin. Wchnschr., 1931, xliv, 1349–1351.

[3] MACNALTY, A. S.: Epidemic diseases of the central nervous system, 1927, Faber and Gwyer, London, p. 193.

encephalitis similar to lethargic encephalitis, but showing important differences in distribution of lesions. The singultus epidemics, a small epidemic of neuro-myelitis optica leading in many instances to blindness, and the notable increase in cases of acute disseminated encephalomyelitis are also quoted by this author as evidence of the increased prevalence of non-lethargic forms of primary encephalitis. To these may well be added the small but highly fatal outbreak in New York City of a condition described by Brown and Symmers [4] as acute serous encephalitis. It is probable that the increased frequency, and at times indeed epidemic character, of so-called serous meningitis [5] in this country and abroad must be looked upon as a part of this general increase in the primary non-suppurative diseases of the nervous system of the general type of encephalitis.

Many of the conditions mentioned in the preceding paragraph are relatively ill-defined pathologically if not clinically. To some degree, however, acute disseminated encephalomyelitis may be excepted from this statement. With the increased incidence of these cases the clinical and pathological resemblance of this disease to an acute stage of multiple sclerosis has stimulated intensive neuropathological and bacteriological research. Pathologically this form of encephalitis is characterized by rather irregularly distributed areas of demyelinization affecting both the gray and the white matter but showing a predilection for the chiasm, the optic tracts and nerves and the subependymal zone adjacent to the walls of the lateral ventricles. The lesions show evidence of a definite inflammatory reaction. This then is a form of primary non-suppurative encephalitis quite distinct in its pathology from lethargic encephalitis which yet has shown, if we may judge from case reports (Redlich [6]), a definitely increased incidence in the last fifteen years.

It is not only in the group of primary encephalitides, however, that a greater frequency of occurrence has been noted. It has long been known that in rare instances non-suppurative encephalitis followed such communicable diseases as measles, chickenpox, smallpox, mumps, whooping cough and scarlet fever. Cases of this type have been reported with such increased frequency in the last decennium as to leave little doubt but what a true increase of incidence has occurred.[7, 8] The clinical symptoms of encephalitis in these cases may in the acute stage bear a resemblance to lethargic encephalitis. Except in cases of post-measles encephalitis, the course is briefer and the mortality lower. In particular they only rarely manifest the

[4] Brown, C. L., and Symmers, D.: Acute serous encephalitis, a newly recognized disease of children, Am. Jr. Dis. Child., 1925, xxix, 174–181.

[5] Eckstein, A., Hottinger, A., and Schleussing, H.: Über die Beziehung der Meningitis serosa epidemica zur Poliomyelitis bzw. Encephalitis epidemica, Ztschr. f. klin. Med., 1931, cxviii, 98–118.

[6] Redlich, E.: Über ein gehäuftes Auftreten von Krankheitfällen mit den Erscheinungen ein Enzephalomyelitis disseminata, Monatschr. f. Psych. u. Neur., 1927, lxiv, 152–184.

[7] Lust, F.: Die paramorbillöse Encephalitis und ihre Folgen, Monatschr. f. Kinderh., 1926, xxxiv, 284–293.

[8] Reimold, W., and Schädrich, E.: Über Enzephalitis im Verlaufe kindlicher Infectionskrankheiten, Jahrb. f. Kinderh., 1921, cxxiii, 229–271.

late development of such conditions as parkinsonism, or myoclonic residuals. Residual palsies are not infrequent. The pathologic findings are best known in the cases following measles, since in these the mortality is high. The disease in this instance is more truly an encephalomyelitis. Its distinguishing histological features are the presence of perivenous inflammatory infiltrations and of well marked perivascular demyelinization. Both the white and the gray matter are involved. These findings differentiate it sufficiently from lethargic encephalitis.

Forms of non-suppurative encephalitis apparently secondary to purulent infections elsewhere in the body, and especially in the head region, have been very frequently reported in recent years, though it is not possible to state definitely that there has been an increase in their incidence. The serous meningitis and the meningo-encephalitis that frequently complicate otitis media [9] are perhaps the commonest examples of the association to which we refer. Striking clinical types of encephalitis may, however, occur in connection with acute purulent sinusitis [10] and occasional cases seem to be secondary to acute tonsillitis, abscessed teeth, bronchitis, and pneumonia.[11] Since the organisms in the primary foci are of pyogenic types while the secondary lesions in the nervous system are non-suppurative, there has developed a tendency for such cases to be referred to as toxic encephalitis. One may place in this same grouping the cases reported as following typhoid fever and dysentery and perhaps the puerperal cases. For the most part the diagnoses of encephalitis, meningo-encephalitis, and encephalomyelitis made in the secondary forms just enumerated are based on clinical rather than pathological criteria.

As further evidence that there has been a general tendency to an increased incidence of all forms of non-suppurative encephalitis, the recent epidemic outbreak of post-vaccinial encephalitis may be cited.[12] Kaiser has found in the literature descriptions of an epidemic of nervous affections following vaccination, which occurred in Bohemia in 1801 and 1802. Since that time, however, no outbreak occurred until 1924. In that year the appearance of cases in England and on the Continent was noted, and up until 1931 when the epidemic was definitely subsiding, over 600 cases had been reported in Great Britain, Holland, Germany, Norway, Austria, and other European countries. In 1928, 1929 and 1930, forty-one cases were observed in the United States. Not only the striking increase in cases, but also the unequal distribution of cases in different communities in the various countries, points toward the true epidemic character of the disease. In one city in the United States there occurred five cases among 5,000 vaccinated children, whereas, the general incidence may be approximated as one in

[9] YERGER, C. F.: Acute toxic meningo-encephalitis of otorhinogenic origin, Arch. Otolaryngology, 1925, i, 198–208.

[10] PINCOFFS, M. C.: Benign cerebral manifestations of sinusitis, Trans. Am. Climat. and Clin. Assoc., 1927, xliii, 215–220.

[11] GRINKER, R. R., and STONE, T. T.: Acute toxic encephalitis in childhood: a clinico-pathologic study of thirteen cases, Arch. Neur. and Psych., 1928, xx, 244–274.

[12] ARMSTRONG, C.: Post-vaccination encephalitis, ANN. INT. MED., 1931, v, 333–337.

300,000. It has been clearly shown that vaccine contamination cannot explain this phenomena. The encephalitis or encephalomyelitis, which develops as a rule from 10 to 13 days after the vaccination, presents various striking clinical pictures which, however, would not serve to differentiate it from the other forms of non-suppurative encephalitis. The mortality has varied in different countries between 17 and 70 per cent. Those who survive may exhibit residual palsies for some time, but for the most part permanent sequelae have been notably rare. Pathologically the disease has been shown to be an encephalo-myelitis with histological features which are not distinguishable from those seen in the similar cases following measles.

The increase of these various forms of encephalitis has not failed to stimulate a search for some factor common to them all and of a nature to have been affected during these last fifteen years by some general epidemiologic influence. It cannot be said that a solution has been found, but the attempts to show that these encephalitides may all be attributable to neurotropic filtrable viruses are of the greatest interest.[13, 14, 15] The case may be summarized as follows: Innumerable attempts at the isolation of a bacterial incitant have yielded mostly negative findings. In a few hands such attempts have resulted in the isolation of streptococci from the brain substance of cases of encephalitis, but even the chief proponents of the streptococcus as an etiological agent have been forced to assume the existence of a filtrable form of this organism. Up to the present time the evidence for bacterial causation is not convincing. On the other hand there is a significant resemblance between the histologic pathology of lethargic encephalitis and that of poliomyelitis, a known virus disease; and moreover, the lesions found in these two diseases in man are similar to those found in certain known virus diseases in animals. In addition to the pathologic resemblance there are certain epidemiologic features which are common to both poliomyelitis and lethargic encephalitis. In particular is this true of the rarity of instances of transmission directly from one person to another. On these grounds there has been a fairly general assumption that lethargic encephalitis is a virus disease.

Direct search for the virus has usually been unsuccessful. In a few instances a virus capable of producing an encephalitis in guinea pigs in series has been obtained from human encephalitis material. The guinea pig encephalitis resembled that which can be produced by the herpes virus in these animals and did not resemble human encephalitis. These findings may be explained in two ways. It is known that man frequently is a carrier of the herpes virus in a latent form. The virus has even been recovered from the spinal fluid of patients exhibiting no evidence of any disease attributable to it. It is also known that during guinea pig transmissions of

[13] RIVERS, T. M.: Relation of filtrable viruses to diseases of the nervous system, Arch. Neur. and Psych., 1932, xxviii, 757–777.

[14] GOODPASTURE, E. W.: Herpetic infection with especial reference to involvement of the nervous system, Medicine, 1929, viii, 223–243.

[15] ZINSSER, H.: The present state of knowledge regarding epidemic encephalitis, Arch. Path., 1928, vi, 271–301.

herpes virus the virus may become neurotropic and produce encephalitis. The simplest explanation then would seem to be that the very rare cases of human lethargic encephalitis from whose brain substance the herpes virus was obtained were merely carriers of this virus. There are those, however, who prefer as an explanation the more complicated assumptions, first that a human neurotropic strain of the herpes virus exists which, contrary to the human cutaneous strain, is very difficult to transmit to guinea pigs, and secondly that this neurotropic virus causes in man a type of encephalitis which is histologically quite dissimilar to that which it causes in guinea pigs. The decision as to the true part played by the herpes virus will probably have to await the next epidemic. It must be pointed out that it remains quite possible that another virus entirely may be the cause of lethargic encephalitis.

In the group of the secondary encephalitides it seems significant that the diseases which are most commonly followed by encephalitis (measles, varicella, mumps, and of late vaccinia) are also those in which a virus etiology has been either suspected or proved. In post-vaccinial encephalitis, however, in spite of numerous attempts it has only very rarely been possible to recover the virus of vaccinia from the brain substance. Proof of the virus nature of the encephalitis following these communicable diseases is still entirely lacking.

In those forms of encephalitis which are secondary to known bacterial infections such as otitis media, sinusitis, pneumonia, etc., it might seem unreasonable to invoke the possible action of viruses. However, it is known that many types of infection in man will lead to the appearance of herpetic vesicles which have been shown to contain active herpes virus. The intercurrent infection is held to have activated the latent virus which then manifests itself by the production of typical skin lesions. If the latent virus had neurotropic qualities, or if the bacterial toxins did preliminary damage to the nervous tissues then the bacterial infection in a virus carrier might be followed by a virus encephalitis.

The known virus diseases in man and those most reasonably suspected of being such are for the most part especially susceptible to epidemiological influences; and if in time to come the present interesting hypotheses as to the virus etiology of the various forms of encephalitis are shown to be well founded we may find therein an explanation of the apparent epidemic increase of all forms of encephalitis during the last fifteen years.

REVIEWS

Diseases of the Heart. By WILLIAM D. REID, M.D., F.A.C.P. 105 pages. The Graphic Press Printers, Newton, Massachusetts. 1933. Price, $.65.

This is a small, paper-bound volume of 105 pages. The author has felt that students should have available some small book, more readily presenting the more important facts in regard to the symptomatology, diagnosis, prognosis and treatment of heart disease than is at present in existence, and, in his own words, the present volume is to be compared possibly to a "laboratory manual."

There is a valuable chapter on history taking in heart disease; and due stress is laid on the value of a well taken history. The more important physical signs of various types of heart disease are clearly presented. There is a tabulation of the information to be obtained from X-ray studies. Short references only are made to the electrocardiogram and other laboratory findings in heart disease. The author includes a table for immediate reference in the diagnosis of the arrhythmias. Prognosis and treatment are briefly treated.

The reviewer questions whether such short cuts to knowledge are of general value. They are no doubt helpful to the students who can use the summary in conjunction with the personal teaching of its author. For these memory will reclothe the bare bones with flesh but for others it must remain a skeleton.

W. S. L., JR.

Gastric Anacidity. Its Relation to Disease. By ARTHUR L. BLOOMFIELD, M.D., Professor of Medicine, Stanford University, San Francisco; and W. SCOTT POLLAND, M.D., Instructor in Medicine, Stanford University, San Francisco. The Macmillan Company, New York, 1933. Price, $2.50.

In this book the authors have presented facts about gastric anacidity which have been culled entirely from the original sources. They have exposed a number of misconceptions which have been passed on from time to time in the literature. It is hard to restrain oneself from the use of superlatives in an account of this volume. The entire subject is covered in a stimulating, exact and highly readable manner.

Misconceptions relating to the use of the term combined acidity, to the so-called hypochromic anemias, and to certain proposed etiological factors in anacidity are discussed in full. The demonstration of the various concentrations of electrolytes in the gastric juice is particularly satisfying. The authors have carefully sifted out the wheat from the chaff in their discussion of the various diseases with which gastric anacidity is commonly associated.

There is so much new, so much sane, and so much enlightening material in the book that one has no hesitation in recommending it to all students of medicine.

L. M.

A Handbook of Pulmonary Tuberculosis. By CARL V. VISCHER, M.D., F.A.C.P.; with a chapter on pulmonary tuberculosis and the cardiovascular system by LOWELL L. LANE, A.B., M.D. xi + 199 pages; 13 × 20 cm. Robert F. Rapp, Collingswood, N. J., 1932.

This small book containing 189 pages of text was written by the author shortly before his death, largely from the notes of his lectures to the students of Hahnemann Medical College of Philadelphia and to nurses. It is a brief systematic account of the chief features of pulmonary tuberculosis, etiology, symptoms, clinical forms, methods of diagnosis, complications, and treatment. The pathology of the disease is presented only incidentally.

Such a clearly written schematic account conforming for the most part to present day standardized terminology, classifications, and diagnostic and therapeutic methods should be of value especially to students, nurses and social workers.

M. C. P.

The Common Causes of Chronic Indigestion. Differential Diagnosis and Treatment. By THOMAS C. HUNT, B.A., D.M.(oxon), M.R.C.P.(Lond.) William Wood and Co., Baltimore, 1933. Price, $4.25.

As its title indicates, this book deals with the more common causes of indigestion. It does not in any way pretend to be an exhaustive survey of the various etiological explanations of the multitudinous gastrointestinal pathological conditions, nor does it attempt to detail the various unusual intra-abdominal conditions which may also cause indigestion.

The subject is treated in 13 chapters which are somewhat irregularly arranged but which may be roughly divided into two main categories: organic diseases of the stomach, gall-bladder and appendix: and functional diseases of the stomach and colon. Such topics as the relationship of the cardiovascular system to indigestion, alcohol in digestion, and indigestion in old age do not come under these headings and have been treated separately. The first of these subjects is especially well handled.

In the interpretation of the symptoms of the ulcerative lesions of the stomach and of cholecystitis, the author shows himself fully cognizant of the immense amount of clinical superstition that has attached itself to these conditions. He stresses the importance of recognizing and treating the underlying factors.

In the chapter on chronic gastritis, which is full, the fundamental pathological findings do not seem to receive adequate consideration and the conclusions are at least open to criticism.

A large part of the book deals with the various functional disorders of the colon. The author's conception of the interrelationship of the psychic and organic bases of these disorders is clearly and interestingly formulated.

A minor criticism may be directed against the overuse of headings throughout the book.

This volume, as mentioned before, cannot in any way be regarded as a reference work; it offers, however, practical conceptions of the conditions discussed, obtained from a working knowledge of the subject and stated in a conservative manner.

L. M.

Practical Hematological Diagnosis. By O. H. PERRY PEPPER, M.D., Professor of Clinical Medicine, University of Pennsylvania, and Assistant Chief of the Medical Clinic, Hospital of the University of Pennsylvania; and DAVID L. FARLEY, Physician to the Pennsylvania Hospital and to the Cooper Hospital, Camden, New Jersey, and Associate in Medicine of the University of Pennsylvania. 562 pages; 16.5 × 23 cm. W. B. Saunders Company, Philadelphia, 1933. Price, $6.00.

There seems to be a real place in medical literature for a monograph on the standard methods of modern hematology and on the purely hematological aspect not only of the diseases of the hemopoietic system but also of other diseases not primarily of the blood. The authors throughout have kept in mind their own introductory statement that hematology is primarily a handmaiden of the clinic and of practice. In Part I, which deals chiefly with hematological methods, only the methods most commonly used in the clinic are described in full; but sufficient details of these are given to serve as a guide to their actual utilization. In their interpretations of the results of these methods the authors' statements are brief and specific. In disputed points references are given to the chief articles supporting the various opinions. The origin, growth and destruction of the morphological elements of the blood are presented in

a surprisingly compact description. It would perhaps have added to the interest of the book, if not to its immediate utility, if a more extended account of the work in this field had been given. In discussing the development and maturation of the red cell no mention is made of the influence exerted upon this process by the intrinsic and extrinsic gastric factors.

Part II is entitled "Hematological Diagnosis of the Diseases of the Hemopoietic System." The title is exact. The clinical aspects of these diseases and the clinical criteria, other than hematological, for their diagnosis are not included. One is confronted with pure hematology. This is so foreign to the clinician's usual way of considering the diagnosis of these conditions as to give the feeling of looking at them with one eye held closed. The limitation in scope, while artificial, is of course intentional. We gain thereby a collection of clear, full and yet succinct descriptions of the diagnostic findings in these diseases which can be derived from the examination of the blood. For quick reference or for comparative studies, this method of presentation is of distinct value.

The hematology of diseases other than those of the hemopoietic system is discussed in Part III. The diseases are arranged alphabetically which assists greatly in ready reference. The collection of data in this section will be of practical assistance to the physician in many diagnostic difficulties.

The more recent work in hematology is well represented. The references have been carefully selected; they cover the classical contributions to the development of the subject and also the latest additions to our knowledge of it.

A noteworthy feature is the ability of the authors to state briefly and fairly the gist of complicated and disputed questions. The book throughout is clearly and interestingly written. Students, laboratory workers and practising physicians will find assistance in its contents.

M. C. P.

Further Studies on the Pharmacology of Certain Phenol Esters with Special Reference to the Relation of Chemical Constitution and Physiologic Action. The Histopathology of Some Neurotoxic Phenol Esters. By MAURICE I. SMITH, Principal Pharmacologist, E. W. ENGEL, Special Expert and E. F. STOHLMAN, Junior Pharmacologist, National Institute of Health, U. S. Public Health Service, Washington. v + 69 pages; 24 × 15 cm. United States Government Printing Office, Washington, D. C., 1932. Price, 10 cents.

The wave of so-called ginger paralysis which occurred in several parts of the United States in 1930 interested the Institute of Health in the investigation of the toxicological and pharmacological nature of the phosphoric acid ester of ortho-cresol. This substance had been used as an adulterant in the extracts of ginger responsible for the poisoning.

In an effort to establish the relation of chemical constitution and physiological activity, the investigators examined twelve esters related to ortho-cresol-phosphate. The formulas and certain physical constants of the compounds are set forth in the publication.

Various types of laboratory animals were used in the examination of the compounds. The generally used avenues of drug administration were employed. Of striking interest is the fact that, in cats, following the subcutaneous injection of the meta- and para-phosphoric acid esters of cresol practically no toxic symptoms were produced. The ortho-isomer, however, produced a typical syndrome of bilateral and symmetrical flaccid paralysis of the distal muscles of the hind legs.

The paper contains graphs showing the rate of hydrolysis of various cresol esters under different chemical conditions.

The section devoted to the histo-pathology of the cresol esters is illustrated by

microphotographs. It is shown that the neurotoxic esters of phenol have a strong affinity for the anterior horn cells. This action is compared with that of the virus of poliomyletis upon the gray matter of the cord.

The publication represents a fundamental investigation of pharmacological nature, interestingly written and containing material of special medical interest.

J. C. K., Jr.

American and Canadian Hospitals. Edited by James Clark Fifield, with the co-operation of the American Hospital Association. 1560 pages; 21 × 27 cm. Midwest Publishing Company, Minneapolis. 1933. Price, $10.00.

The Editor and the American Hospital Association are to be congratulated upon the completion and publication of this valuable compilation of informative data concerning the hospitals of the United States and Canada. The material is arranged geographically and alphabetically according to the system employed in the Medical Directory of the American Medical Association. The hospitals in all the extra-territorial possessions of the United States and those in Newfoundland and Labrador and in the Northwest and Yukon Territories are included.

The chief data given include: the character of the hospital, general or special; the number of departments or services; the special facilities; the history of its construction; the number of beds; the rates; the financial status; the average number of patients; the constitution of the staff, including the house staff; the training school; the ownership of the hospital; the governing body; the name of the superintendent and of the director of the training school.

Interesting historical sketches of all the associations and leagues devoted to hospital problems precede the main matter of the book; and in the Appendix information is added concerning all the religious orders in the hospital field; the important endowments or funds devoted to health purposes; the national health associations; the U. S. Public Health Service; the Veterans Administration, etc.

Such information will be of the greatest value to all engaged in hospital work who may wish to make comparative studies of other hospitals or of problems of hospitalization. It will no doubt be of fundamental aid to the work of the American Hospital Association. It will be of assistance to physicians generally who may wish to know of hospital facilities at a distant point. Medical students may find it of value in connection with a search for internships, and house officers may consult it in determining upon a location in which to practise. There is no doubt but what the makers of all hospital equipment and supplies will use it freely. It will surely become a standard reference work of great value.

The appearance of the volume, the binding and typography are a credit to the publishers.

M. C. P.

COLLEGE NEWS NOTES

Dr. Walter L. Bierring (Fellow and Regent of the American College of Physicians) was elected President-Elect of the American Medical Association at its last annual meeting in Milwaukee during June.

Dr. Bierring has had a significant career in medical organization. He has been President of the Iowa State Board of Medical Examiners, President of the National Board of Medical Examiners, President of his County and State Medical Societies, President of the Alpha Omega Alpha, honorary medical fraternity, and is President of the Iowa State Board of Health. He has been a Fellow of the American College of Physicians since 1928, and a member of its Board of Regents since 1930.

Dr. John H. Musser (Fellow and Regent), New Orleans, was elected Vice-President. Dr. Nathan B. Van Etten (Fellow), New York City, was elected Vice-Speaker. Dr. James S. McLester (Fellow and Regent), Birmingham, Ala., was appointed a member of the Committee on Medical Education and Hospitals, and Dr. J. E. Paullin (Fellow), Atlanta, Ga., was appointed a member on the Council of Scientific Assembly.

Dr. Louis Faugeres Bishop, Sr. (Fellow), New York, N. Y., was elected President of the American Therapeutic Society for the years 1933–1934, at the annual meeting of that Society held in Milwaukee, Wis., June 9 to 10, 1933.

Dr. Edward B. Krumbhaar (Fellow), and Dr. William D. Stroud (Fellow and Treasurer), both of Philadelphia, were elected President and Vice-President, respectively, of the Philadelphia Heart Association at its annual meeting in April.

Dr. Paul Dudley White (Fellow), Instructor in Medicine at Harvard University Medical School, was the speaker.

The May issue of *Radiology* was dedicated to Dr. Albert Soiland (Fellow), Los Angeles, Calif., "in acknowledgment of his achievements in radiology and in recognition of his sixtieth birthday." Dr. Soiland was the founder of the American College of Radiology, and is at present a member of the House of Delegates of the American Medical Association.

Under the Presidency of Dr. Adolph Sachs (Fellow), of Omaha, the Nebraska State Medical Association held its Sixty-fifth Annual Meeting in Omaha, May 23 to 25, 1933.

Dr. Charles A. Elliott (Fellow), Professor of Internal Medicine at Northwestern University Medical School, Chicago; Dr. H. L. Bockus (Fellow), Professor of Gastro-Enterology, Graduate School of Medicine of the University of Pennsylvania, Philadelphia; and Dr. Walter Clarke (Fellow), Director of Medical Activities, American Social Hygiene Association, New York City, were guests of honor and delivered addresses in their respective fields.

The East Mississippi Medical Society conducted a postgraduate medical institute at Meridian, Miss., June 6 to 9, 1933, inclusive.

Dr. George Herrmann (Fellow), Professor of Clinical Medicine at the University of Texas, Editor of the *American Journal of Syphilis*, Associate Editor of *Laboratory and Clinical Medicine*, and Physician to the John Sealy Hospital, of Galveston, Texas, with Dr. Joseph C. Bloodgood, of Baltimore, Md., conducted lectures and clinics.

At the tenth anniversary meeting of the American Society of Stomatologists, in New York City on April 27, 1933, the CHOMPRET PRIZE was awarded to Dr. Oliver T. Osborne (Fellow), Emeritus Professor of Therapeutics at Yale University School of Medicine, for his "Meritorious contributions to the science of stomatology and for his untiring labors to bring dentistry and medicine to a plane of better understanding and appreciation of their common problems for the good of mankind."

Dr. Anthony Bassler (Fellow), New York City, made the presentation address, as follows:

"The American Society of Stomatologists, together with the International Academy of Stomatology, has therefore deemed it an honor to commemorate the work of this great pioneer in stomatology (Dr. Joseph Chompret) by establishing the CHOMPRET PRIZE, symbolized by a gold medal to be awarded every second year to the deserving person who has made the most outstanding contribution to the progress of stomatology either in the realm of science or in the professional advancement of the stomatologic specialty. This medal will be awarded at the recommendation of the CHOMPRET PRIZE COMMITTEE of the International Academy of Stomatology and the American Society of Stomatologists. . . ."

Dr. James J. Waring (Fellow) has been appointed Professor of Medicine of the University of Colorado. During the past year he was elected Vice-President of the Western Branch of the American Public Health Association, and a Director of the National Tuberculosis Association and member of its Executive Committee.

Dr. James L. McCartney (Fellow), Psychiatrist and Director of Classification, New York State Department of Correction, Elmira Reformatory, has been awarded a grant of $1,000.00 by the Thomas W. Salmon Memorial Committee of the New York Academy of Medicine for investigation on the classification of prisoners and the drawing up of a handbook on classification for use in prisons.

Dr. McCartney for the past two years has been Director of the Classification Clinic at Elmira Reformatory, and is Secretary of the Medical Section of the American Prison Association, as well as a member of the Committee on Case Work and Treatment of the American Prison Association, which is attempting to standardize the scientific examination and care of prisoners in this country.

A report of this Committee is to be given at the forthcoming congress of the association, which is to be held in Atlantic City the second week of October.

Dr. Solomon Solis-Cohen (Fellow), Philadelphia, Pa., received the honorary degree of Doctor of Science at the recent 108th annual commencement at Jefferson Medical College of Philadelphia.

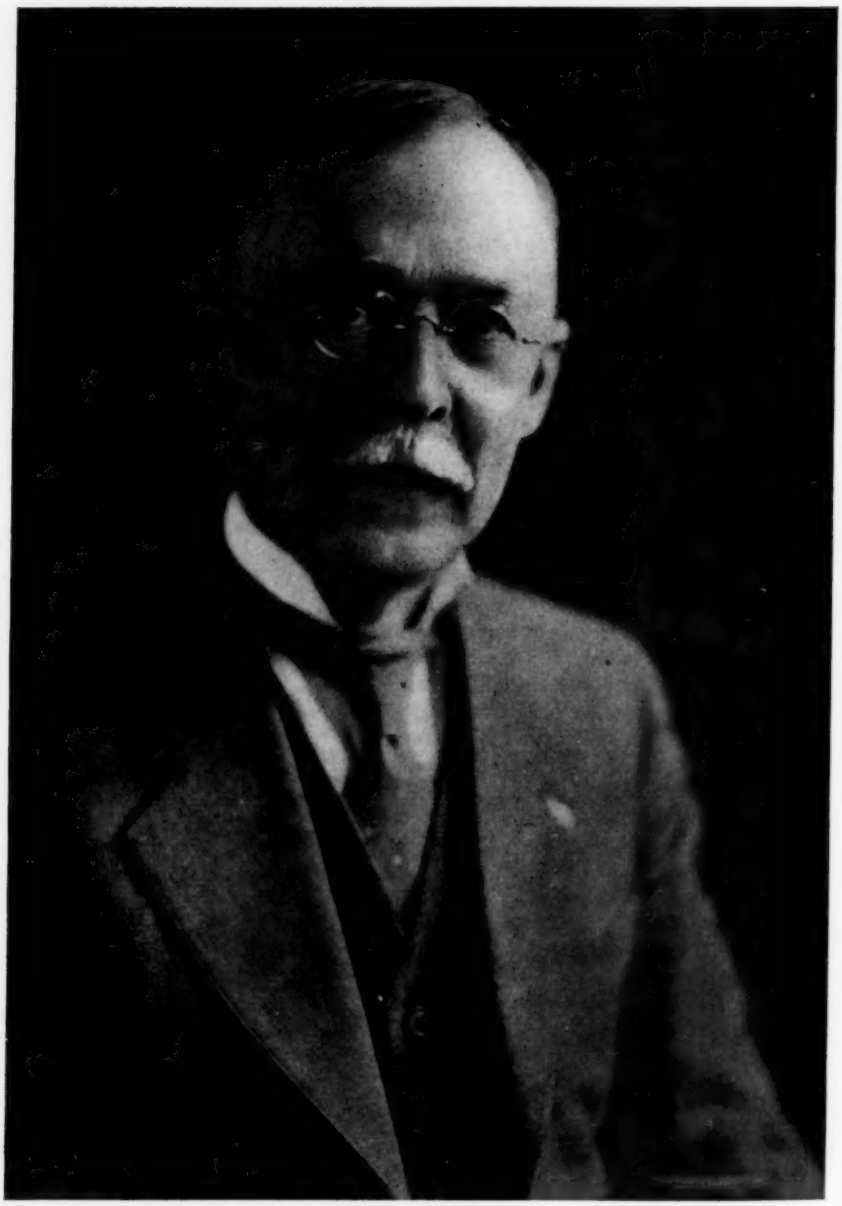
Dr. Solis-Cohen was a graduate of the Class of 1883 of this institution and is Emeritus Professor of Clinical Medicine.

Dr. Albert E. Russell (Fellow), Washington, D. C., has been appointed Chief Surgeon of the U. S. Bureau of Mines.

Dr. Russell addressed the Toledo (Ohio) Academy of Medicine on May 5, 1933, on the subject of occupation and respiratory diseases.

Dr. Samuel E. Thompson (Fellow), Kerrville, Tex., was elected President-Elect of the State Medical Association of Texas at its annual meeting in May.

Dr. G. L. Pinney (Fellow), Hastings, Nebr., was recently elected Vice-President of the Nebraska State Medical Association.



DR. WILLIAM BLAIR STEWART

OBITUARIES

DR. WILLIAM BLAIR STEWART

Dr. William Blair Stewart was of Scotch-Irish descent, son of a physician and grandson of a physician. He was born March 6, 1867, at Middle Spring, Pa., in the Cumberland Valley. Soon after his birth, his family removed to New Brighton, in the western part of the State, where they remained with his maternal grandfather for two years. They removed to Newburg, a hamlet near Middle Spring, where his father practised medicine until 1873. The family then moved into the adjoining town of Newville, which remained his home for many years, and to which he loved to return, in later life, twice a year to renew old acquaintances and to fish in the creek.

Dr. Stewart entered Dickinson College, Carlisle, Pa., receiving the Ph.B. degree in 1887 and the M.A. degree subsequently. His enduring loyalty to his Alma Mater was rewarded forty-five years later by his election to the Vice-Presidency of the Alumni Association of that institution. In 1890 he was graduated with highest honors from the Medico-Chirurgical College of Philadelphia, in which he also served as Instructor in Therapeutics.

After spending the summer of 1890 in Atlantic City as assistant to Dr. Boardman Reed, and seven months on Fairmount Avenue in Philadelphia, he removed to Bryn Mawr, where he practised medicine for three years. In August 1894, he moved to Atlantic City, N. J., as a permanent resident, assisting Dr. Reed at first and later taking over his property at the corner of North Carolina and Pacific Avenues when Dr. Reed retired in 1898. It was here he brought his bride, Florence Elizabeth Giffin, in 1897; here were born his children, Walter in 1898 and Sloan in 1901—both physicians at present—and here he died on July 11, 1933, at the age of sixty-six.

The three great interests in his life were family, society and medicine; intermingling all of which was a pervasive love of and faith in humanity. He made friends readily, but enemies rarely. Friends made were friends retained. His loyalties were strong. He was friend of the child, the elevator boy, the delivery man. There was always some witticism on the end of his tongue, or some bit of humor "up his sleeve"; an unusual ability in ventriloquism often baffled friends and charmed animals. His three grandchildren were his greatest source of pleasure in his latter years. Seldom was there a day when he would miss the noon visit with them.

As evidence of his civic interest, he had been President of the Atlantic City Board of Trade, Director of the Chamber of Commerce, member of the Board of Education, President of the Board of Trustees of the First Presbyterian Church and a Director of the Young Men's Christian Association. One may best quote from an editorial in the *Atlantic City Press:* "Dr. W. Blair Stewart, who died this week, should be long remembered for his upstanding citizenship no less than his high professional rating and worth. Always a conservative, of sound and practical judgment, he was ever to be found working diligently for projects which meant worthwhile

progress for Atlantic City, against projects which smelled of malodorous politics or other civically-destructive influences. . . ." His political faith was always Republican. He was a thirty-second degree Mason and a Knights Templar. In the Atlantic City Rotary Club he had a perfect attendance record for the past eight years, and maintained a keen interest in all the activities of the Club.

He was the author of a textbook on medicine, "A Synopsis of the Practice of Medicine," in his earlier years, and he frequently contributed articles to various medical journals. His medical name first came into local and national prominence in his successful efforts in the late nineties to eradicate the serious menace of typhoid fever from Atlantic City, a menace that has never returned. He was an ex-President of the Atlantic County Medical Society, and had always taken an active rôle in the New Jersey State Medical Society. For many years he was a Surgeon to the Atlantic City Hospital, but later, feeling an increasing fondness for Internal Medicine, he gave up major surgery and worked solely as an internist. He was a former Vice-President of the American Medical Association and one of the early (1916) Fellows of the American College of Physicians. For several years, he had been Chairman of its Board of Governors and a member of the Board of Regents.

Although in the last years of his life he observed the insidious development of coronary disease and myocarditis, especially in the final year, he dreaded the prospects of a life of invalidism, but insisted rather in remaining "in harness" until the end, which came suddenly, as he would have had it.

WALTER B. STEWART, M.D.

DR. THOMAS JEFFERSON McKINNEY

Dr. Thomas Jefferson McKinney (Associate), Champaign, Illinois, died May 27, 1933, in the Kenilworth (Ill.) Sanitarium; aged, 73 years.

Dr. McKinney was born at Muncie, Indiana. He attended the Illinois State Normal University and entered the Medical College of Indiana, from which he received his degree of Doctor of Medicine in 1883. After a few years of practice, he secured the degree of Doctor of Medicine from the Northwestern University Medical School in 1898. He pursued postgraduate training at the Chicago Post Graduate Medical School, the Chicago Policlinic and the New York Post Graduate Medical School. He was a member and former President of the Champaign County Medical Society, a member of the Illinois State Medical Society, and a member of the American Medical Association. He was a teacher in mental and nervous diseases to nurses and President of the Staff of the Burnham City Hospital. He had been an Associate of the American College of Physicians since 1926.